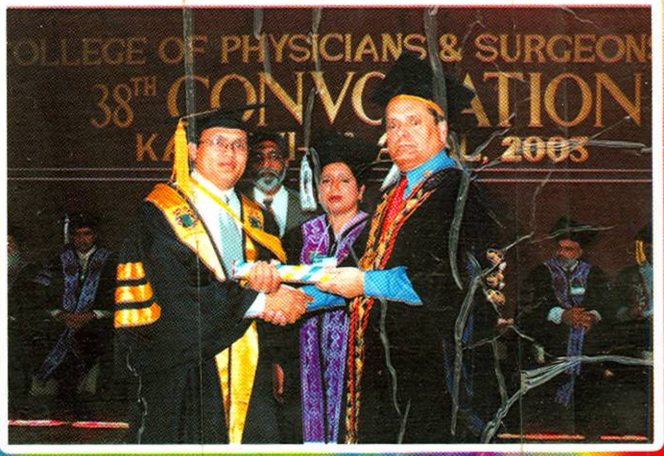
Short Textbook of

MEDICAL DIAGNOSIS AND MANAGEMENT



Mohammad Inam Danish

2006

8th International Edition

JOHAR PUBLICATIONS

SHORT TEXTBOOK OF

MEDICAL DIAGNOSIS AND MANAGEMENT

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One of the best interventionist and Director
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Senior Registrar Karachi Institute of Heart Diseases.

نحمده ونصلي على رسوله الكريم

بسم الله الرحمن الرحيم

Dedicated to

MY PARENTS

May ALLAH rest their souls in Heaven and be Merciful to them as they were to me in my childhood (Amen)

And my honorable professor

DR. MASHOOR ALAM SHAH

Professor of medicine
And Director
Jinnah Post Graduate Medical Center (JPMC)
Karachi

REQUEST TO MEDICAL STUDENTS

- This new edition is rewritten; with significant improvement in **cardiovascular system and hepatobiliary system. Psychiatry** is also included.

- Please do not purchase the pirated book; otherwise you will be the part of cruelty and injustice.

- To discourage piracy please always ask for the **latest edition** and print, you will find some definite changes in every next print.

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PREFACE

- All sections are rewritten and updated according to the new editions of standard books and recent medical journals.
- Medical students will be more able to solve the theory papers with the help of this comprehensive edition.
- Important long and short cases are discussed according to the examination format.
- Protocols of important cases are added so that the residents and house officers will have management guidelines very quickly.
- This publication will prove a quick review of medicine for the postgraduate students.
- This edition will also help the general medical practitioners in diagnosis, selection of investigations and proper management.
- Nursing staff, students of Homeopathic and Tibbe- Unani may also get valuable help from this book.
- Positive criticism is welcomed to improve further.

A quick and comprehensive review book for:

* **Medical students**
* **House officers**
* **Residents**
* **General practitioners.**

Wish you all the best.

Inam Danish

Dr. Inam Danish

Karachi – Pakistan

CONTENTS

FORMULA FOR SUCCESS

Please read the following, it is written to prepare you for a successful life

- Never treat the major illness of your family member because you are not the suitable person who can take appropriate decisions for the patient due to the emotional factors.
- Marry the right person. This one decision will determine more than 90% of your happiness or misery. Do not compromise on it, as you have no chance to get life again for the proper decision.
- Always pray to God to save from single, unmarried or divorced boss, as he/she is unable to realize and consider the problems of married subordinates.
- Work at something you enjoy and that is worthy of your time and talent.
- Be forging of yourself and others.
- Be expressive, because no one can correctly assess the feeling of your heart, say good to good and bad to bad. Express your love and hate.
- Appreciate peoples in their lives for their valuable work; they will not listen when you will speak in their condolence meeting.
- Persistence, persistence, persistence.
- Treat every one you meet like you want to be treated.
- Commit yourself to constant improvement.
- Be loyal, kind, honest and generous.
- Stop blaming others for your failure, find out the reasons and try again.
- Do not transfuse blood (or perform procedures) at night if there is no emergency and until you have all measures of resuscitation. Are you able to manage the complications ?
- You will be surprised on meeting with most of the post holders in our society, as majority of the posts are occupied by inefficient and undeserving persons.
- You will have no space here, until you go abroad, get skill and then come back. I appreciate the Western teachers who are not miser in transferring the skill.
- In so- called teaching system you will listen long lectures but no one will allow you to learn the procedures through which you may be able to earn.
- Give your children two gifts, a home and professional education.
- Do not mention the problems of your family to anyone, because every one is not loyal and every one is not your friend forever.
- Don't do any thing that wouldn't make your Mom proud.

Wish you a happy and successful life

CARDIOVASCULAR DISEASES 1

For:

Angiography & Angioplasty

<u>Please Consult</u>

Dr. M. Inam Danish

CHEST PAIN

Chest pain is one of the most important emergencies; therefore it is necessary to evaluate chest pain thoroughly. It could be as serious as myocardial infarction (MI) or just muscular pain. Always think first and rule out life threatening conditions such as myocardial infarction, aortic dissection, pulmonary embolism and pneumothorax.

History is very important, ask whether it is acute and ongoing pain, recurrent or episodic pain, or persistent pain even for days.

CAUSES OF CHEST PAIN

Cardiac	Vascular
Coronary artery disease such as angina, MI Aortic stenosis Pericarditis Hypertrophic cardiomyopathy	Pulmonary embolism Aortic dissection
Pulmonary	**Gastrointestinal**
Pleuritis Pneumonia Pneumothorax	Reflux esophagitis Esophageal spasm Peptic ulcer
Musculoskeletal	**Others**
Cervical disc disease Arthritis of shoulder or spine Costochondritis	Disorders of breast Herpes Zoster Emotional

CHEST PAIN DUE TO ANGINA PECTORIS

Angina means discomfort. Angina pectoris is usually described as heaviness, pressure, squeezing or sensation of constriction in the chest, but it may be described as aching or burning pain, difficulty in breathing or even an indigestion (gas trouble). In order to take good history you should know the difference between stable and unstable angina.

Anginal chest pain may be typical or atypical.

Typical chest pain

- Typical pain of stable angina is the pain that develops gradually during exertion, after meal, with anger, excitement, frustration and other emotional states; it is not precipitated by coughing, respiratory movements or change in position.
- Anginal pain typically resolves within 5 to 30 minutes. More prolonged pain represents myocardial ischemia while more prolonged pain without evidence of myocardial ischemia suggests a non-cardiac pain.
- Anginal pain disappears usually after rest or within 5 minutes when sublingual nitroglycerine (Angised) is used.
- Angina typically occurs in retrosternal region, anteriorly across the midthorax. It may radiate to or rarely occur alone in the interscapular region, arms, shoulders, teeth, or abdomen.

❑ All these features of pain represent ischemic pain due to stable angina, while the pain of unstable angina occurs at rest, may be atypical and less responsive to nitroglycerine.

Atypical chest pain

Atypical chest pain may be due to ischemic heart disease (especially unstable angina) however it is less likely to be cardiac in origin. Atypical chest pain may present as following:

- Sharp or knife- like pain brought on by respiratory movements or cough (pleuritic pain).
- Pain that has primary location of discomfort in the middle or lower abdominal region.
- Pain that may be localized at the tip of one finger, particularly over the left ventricular apex.
- Pain produced with movement or palpation of the chest wall or arms.
- Constant pain that persists for many hours.
- Very brief episodes of pain that last a few seconds or less.
- Pain that radiates into the lower extremities.

CHEST PAIN DUE TO MYOCARDIAL INFARCTION

Pain of myocardial infarction is similar to angina in distribution but it is of longer duration and is usually of greater intensity. In contrast to stable angina it is not relieved by rest or sublingual nitroglycerine. It may be accompanied by nausea, perspiration and hypotension.

Diagnosis and plan of management

- *History:* History is very important, ask about risk factors for MI such as hypertension, smoking, diabetes, dyslipidemia and strong family tendency. Decide whether the pain is typical or atypical, acute ongoing pain, recurrent or persistent pain.
- *Examination* is usually unremarkable.
- *ECG:* ST depression or elevation.

If clinical suspicion of myocardial ischemia is strong and ECG is normal then keep the patient in observation for 6-12 hours, perform serial ECGs and check cardiac enzymes. After this period further cardiac testing with ETT, or thallium scan helps in making the diagnosis.

Following investigations may be considered to identify the cause of chest pain depending on clinical assessment:

- ECG
- Cardiac enzymes (CK-MB, Troponin T or Troponin I)
- X- ray chest
- X- rays of spine, shoulder or rib
- Echocardiogram
- CT chest
- Upper GI endoscopy

PATIENT EVALUATION AND PLAN

Always rule out life threatening conditions such as myocardial infarction, aortic dissection, pulmonary embolism and pneumothorax.

History is very important, ask about risk factors for MI such as hypertension, smoking, diabetes, dyslipidemia and strong family tendency. Decide whether the pain is typical or atypical. For pulmonary embolism ask about prolonged bed rest, DVT, use of oral contraceptives and valvular heart disease. History of heartburn and food regurgitation may indicate reflux esophagitis. Ask about any emotional problem. Sudden chest pain with shortness of breath, especially in patients of asthma, tuberculosis and COPD may indicate pneumothorax. While examining the patient auscultation of lung and heart may be helpful. Local tenderness indicates musculoskeletal disorder.

CHEST PAIN DUE TO PERICARDITIS

- Visceral pericardium and most of the parietal pericardium is insensitive to pain, therefore pain associated with pericardium is believed to be due to inflammation of adjacent parietal pleura. Pain due to non-infectious causes such as MI or uremia is mild while infectious pericarditis causes more severe pain due to spread of infection to the neighboring pleura.
- Pain due to pericarditis may be felt at the tip of the shoulder, neck, anterior chest, upper abdomen or back.
- Pericardial pain is aggravated by cough and deep inspiration because of pleural irritation, change in posture and swallowing. It becomes sharper and more left- sided in supine position and milder when patient sits upright and leans forward.
- In some patients pericardial pain is steady retrosternal discomfort mimicking the pain of myocardial infarction.

CHEST PAIN DUE TO PULMONARY EMBOLISM

Infarction of a segment of lung that is adjacent to the pleura commonly irritates pleural surface and causes chest discomfort, it may resemble the pain of myocardial infarction.

CHEST PAIN DUE TO ESOPHAGEAL CAUSES

Esophageal spasm due to reflux esophagitis causes squeezing pain that mimics pain of MI. It may have similar pattern of distribution. History of heartburn

and food regurgitation are important clues. A number of children come to cardiac emergency with chest pain that is usually due to esophageal spasm as result of eating groundnut in the form of sweat supari, pan or gutca. We can only pray to God to save our children as the government is not interested to stop such health-killing business.

CHEST PAIN DUE TO MUSCULOSKELETAL DISORDERS

Localized tenderness is common. Pain may be sharp, lasting for few seconds or it may be dull that persists for hours or even days. Pain is variable in site and intensity; there is no definite pattern. It may vary with posture or movement, but does not cease instantly on rest. Pain due to cervical spondylosis is very common.
Local tenderness over rib or costal cartilage is usually present.

CHEST PAIN DUE TO AORTIC DISSECTION

Hypertension and Marfan's syndrome are the most common predisposing factors. Patient is usually old presenting with severe tearing chest pain radiating to interscapular region, not responding to anti - anginal treatment. Pulse may be unequal. Features of cardiac temponad or acute aortic regurgitation may be present. Chest x-ray may show wide mediastinum. Transesophageal echocardiogram (TEE), CT or MRI are helpful in diagnosis.

CHEST PAIN DUE TO EMOTIONAL CAUSES

Emotional disorders may cause chest discomfort in the form of chest tightness, lasting for half an hour or more that is unrelated to exertion. It may be sharp and very brief and located near the left nipple. This type of pain is also called "precordial catch" effort syndrome or Da Costa's syndrome". Emotional strain may be evident or not. This type of pain is common in females of our society. However never underestimate the young population because this chest pain may be a real problem as a result of mitral valve prolapse (MVP), aortic stenosis or hypertrophic cardiomyopathy.

Therefore always rule out all possibilities before declaring pain due to emotional disturbance, hysteria or malingering.

DYSPNEA

Dyspnea or Shortness Of Breath (SOB) is an abnormal awareness of respiration. Dyspnea in heart disease is precipitated or exacerbated by exertion but may occur at rest. It results from elevated left atrial and pulmonary venous pressures or hypoxia, as a result of left ventricular systolic or diastolic dysfunction or valvular obstruction.

Grading of dyspnea

The New York Heart Association has graded dyspnea ranging from grade 1-4. Always describe dyspnea with grading because it indicates functional class of patient and severity of the disease. Always describe dyspnea with NYH grading.

The New York Heart Association functional and therapeutic classification applied to dyspnea.	
Grade 1	No breathlessness
Grade 2	Breathlessness on severe exertion.
Grade 3	Breathlessness on mild exertion
Grade 4	Breathlessness at rest.

Types of cardiac dyspnea

- Acute pulmonary edema
- Angina equivalent
- Chronic heart failure

Acute pulmonary edema

Acute pulmonary edema develops from a major event such as acute myocardial infarction in previously healthy heart or minor event such as atrial fibrillation in a previously diseased heart.
Patient suddenly develops shortness of breath, distress, agitation and cyanosis with coughing and wheezing. Sputum may be profuse, frothy and blood – streaked or pink. Heart auscultation reveals crepitations and rhonchi.

Angina equivalent

When shortness of breath is the dominant or sole feature of myocardial ischemia instead of chest pain, this is called angina equivalent. Some patients especially old people present ischemia with shortness of breath without features of pulmonary edema (no prominent crepitation). ECG shows ST changes and treatment of angina relieves shortness of breath even without diuretics.

SHORTNESS OF BREATH (DYSPNEA)		
System	**Acute dyspnea at rest**	**Chronic exertional dyspnea**
Cardiovascular	• Acute pulmonary edema • Myocardial ischemia (angina may present just with dyspnea and this presentation is called angina equivalent)	• Chronic heart failure • Myocardial ischemia (angina may present just with dyspnea and this presentation is called angina equivalent)

Chronic heart failure

- ***Orthopnea*** is dyspnea that occurs during supine position (recumbency) as a result from increase in venous return.
- ***Paroxysmal Nocturnal Dyspnea (PND)*** is the shortness of breath that occurs abruptly 30 minutes to 2 hours after going to bed and is relieved by sitting up or standing up.

PALPITATION

Palpitation is an unpleasant awareness of the forceful or rapid beating of the heart. Patients describe it as pounding, jumping, racing or irregularity of heart beat. Palpitation can develop by change in heart rate, rhythm, ectopic beats, compensatory pauses, augmented stroke volume due to valvular regurgitation, high cardiac output states, all forms of tachycardia and sudden bradycardia.

Sinus tachycardia may be due to anxiety, anemia, fever or drugs etc while the paroxysmal tachycardia is usually due to SVT, atrial flutter or fibrillation. When palpitation begins and ends abruptly it is often due to a paroxysmal arrhythmia while the gradual onset and cessation of attack suggest sinus tachycardia or anxiety state.

Palpitation = slow, fast or irregular rhythm

Premature (ectopic) beats

Recurrent but short-lived bouts of an irregular heart beat are usually due to atrial or ventricular ectopic beats. Patients describe it as a dropped beat because the premature beat is followed by a pause before the next normal beat which is more forceful as a result of longer diastolic filling period. Most of the time it is related to anxiety and aggravated by chocolate and excessive intake of tea.

Paroxysmal tachycardia

Bouts of very rapid heart beat (>120/min) starting abruptly and terminating suddenly result from paroxysmal supraventricular (atrial or junctional) tachycardia or ventricular tachycardia. Paroxysmal supraventricular tachycardia (SVT) and paroxysmal atrial fibrillation are common causes.

Some patients feel tachycardia on standing from sitting position associated with a mild drop in blood pressure and symptoms of dizziness. These patients have a form of autonomic dysfunction termed the *postural orthostatic tachycardia syndrome (POTS).*

Paroxysm of tachycardia especially when prolonged may be associated with syncope, presyncope, dyspnea or chest pain. In patient's evaluation and diagnosis, measure blood pressure, check pulse and perform an ECG.

Reassurance, avoidance of stress, coffee and treatment with beta - blockers are usually enough to control the symptoms.

Bradycardia

Although generally palpitation means tachycardia, sometimes patients of heart block and bradycardia also complain of palpitation.

Ghabrahat is very commonly used Urdu term that patients describe for restlessness and in majority of cases due to tachycardia, sometimes due to bradycardia or irregular rhythm.

PERIPHERAL EDEMA

Pedal and sacral edema in cardiac patient results from heart failure (usually as a result of right or combined right and left heart failure) as a result of salt and water retention. Other cardiac causes of edema are constrictive pericarditis and cardiomyopathy. Calcium channel blockers also produce pedal edema. None-cardiac causes are peripheral venous insufficiency, venous obstruction, nephrotic syndrome, cirrhosis or idiopathic.

DIFFERENTIAL DIAGNOSIS OF PERIPHERAL EDEMA

- Cardiac failure: right heart failure, constrictive pericarditis and cardiomyopathy.
- Chronic venous insufficiency (Varicose veins)
- Hypoalbuminaemia
  - Nephrotic syndrome
  - Liver cirrhosis
  - Protein-losing enteropathy
- Drugs
  - Retaining sodium: non steroidal anti-inflammatory drugs NSAIDs)
  - Increasing capillary permeability e.g nifedipine, amlodipine
- Idiopathic (women > men)
- Chronic lymphatic obstruction

SYNCOPE

Syncope is a transient loss of consciousness resulting from an insufficient blood supply to the brain. Presyncope is the condition in which patient feels lightheadedness while in syncope there is sudden loss of consciousness. The most common types are vasovagal syncope, postural syncope, drug- induced syncope and cardiac syncope.

VASOVAGAL SYNCOPE (COMMON FAINT)

- Vasovagal syncope is caused by excessive vagal activation and decreased venous return which is initiated by prolonged standing, large meal, stressful and painful stimuli such as fright, pain, unpleasant sights, exhaustion, hot atmosphere etc.
- It results from reduced venous return to the heart, at the same time there is sympathetic stimulation that leads to vigorous contraction of the relatively under-filled ventricles stimulating reflex by stimulating ventricular mechano- receptors. This produces parasympathetic (Vagal) activation and sympathetic withdrawal causing bradycardia, vasodilatation or both.
- There are some variants of vasovagal syncope such as cough syncope and micturition syncope.
- The patient appears pale, there is usually slow pulse, low blood pressure and dilated pupils.

Diagnosis

Head–up tilt testing is a test to diagnose vasovagal syncope. In this test patient is asked to lie on a table that is then tilted on an angle of 70^o for up to 45 minutes while the ECG and blood pressure are monitored. A positive test is characterized by profound bradycardia and/ or hypotension.

Treatment

- Beta–blockers are helpful by inhibiting the initial sympathetic activation.
- Dual chamber pacemaker if bradycardia is predominant.

POSTURAL SYNCOPE

Postural syncope results from failure of normal compensatory mechanism of baroreceptors which normally adjust heart rate and peripheral resistance in response to changes of posture. Decreased peripheral resistance causes vasodilatation and produces hypotension which is known as postural hypotension (decline in systolic pressure more than 10mm Hg immediately upon rising from supine to standing position is known as postural hypotension). This sudden hypotension reduces cerebral blood flow, resulting in syncope. It is a common cause of OPD visit by the patients taking ACE inhibitors and diuretics.

Predisposing factors

- Old age
- Parkinson's disease
- Diabetics and other patients with autonomic neuropathy
- Blood loss or hypovolemia
- Drugs e.g. Vasodilators, beta-blockers, antidepressants and diuretics.

Treatment

- Withdraw or reduce the dose of responsible drug.
- Ask the patient to wear elastic stockings.
- Get up slowly from the bed.
- NSAIDs and fludrocortisone may be required.

CARDIOGENIC SYNCOPE

It results from profound hypotension due to combination of a reduction in cardiac output and drop in peripheral vascular resistance or arrhythmia.

Causes

Tachyarrhythmias

- Ventricular tachycardia
- Supraventricular tachycardia

Bradyarrhythmias

- Sick sinus syndrome
- Heart block

Mechanical obstruction

- Myocardial infarction
- Aortic/ pulmonary stenosis
- Pulmonary hypertension/ embolism
- Atrial myxoma/ thrombus
- Hypertrophic obstructive cardiomyopathy.
- Fallot's tetralogy
- Stuck up prosthetic valve

INVESTIGATIONS IN CARDIAC DISEASES

ECG

ECG is useful to detect the following abnormalities

- Cardiac arrhythmias
- Conduction defects
- Myocardial infarction or ischemia
- Myocardial hypertrophy
- Electrolyte imbalance
- Toxicity of certain drugs

ECG interpretation is not much difficult, it is very important tool of investigation; therefore spend a lot of time in ECG reading during posting in cardiology unit. If ECG interpretation is weak it will become difficult for a physician to deal with cardiac emergencies with accuracy. Unfortunately in Government Hospitals most of emergency medical officers are posted from skin, surgery, neurology and other specialties who are not trained in ECG reading, sometimes they are even unable to recognize cardiac emergency that results in loss of patient's life. This practice will be continued until merit (not influence) becomes the criteria for selection of medical superintendents. Be a safe physician, learn ECG.

There is nothing difficult in medical education except to find out sincere teachers who have teaching skills and who are generous in transferring the practical knowledge to their students (unfortunately most of them are not → reason → selection not based on merit).

CHEST X-RAY

Heart size

Heart size can be reliably assessed only from PA view of chest x-ray, because in AP view cardiac shadow is large. The maximum transverse diameter of the heart is compared with the maximum transverse diameter of the chest measured from inside of the ribs; this is called cardiothoracic ratio (CTR). It should be less than 50%. Cardiomegaly and pericardial effusion cause an increase in cardiothoracic ratio.

- Pericardial effusion produces globular shadow.
- Left atrial dilatation manifests as prominence of left atrial appendage on the left heart border and a double atrial shadow to the right of the sternum (double right heart border).
- Left ventricular enlargement manifests as increased CTR and an increased convexity of the left heart border.
- Right atrial enlargement manifests as projection of right border of heart into the right lower lung field.
- Right ventricular enlargement manifests as increased CTR and an upward displacement of the apex of the heart.
- Enlargement of pulmonary artery manifests as a prominent bulge on the left heart border below the aortic knuckle.

Calcification

X-ray chest may show calcification of pericardium, valves, aorta and myocardium.

Lung fields

Lung fields may indicate pulmonary hypertension by enlargement of hilar vessels e.g. enlarged right lower lobe artery. Kerly's B lines and pleural effusion may be present in cardiac failure.

ECHOCARDIOGRAPHY

It is a sensitive method for determination of :

- Size of all four chambers of heart.
- Left ventricular function (ejection fraction).
- Regional wall motion abnormalities due to myocardial infarction, ischemia.
- Complications of myocardial infarction such as papillary muscle dysfunction, mitral regurgitation, VSD, left ventricular aneurysm and left ventricular thrombus..
- Structural valve abnormalities e.g. stenosis and regurgitation.
- Cardiac output.
- Ventricular hypertrophy
- Pericardial effusion.
- Atrial and ventricular septal defects and other congenital defects.

Types of echocardiography

Two-dimensional real time echocardiography

This type of echocardiography is particularly valuable for detecting wall motion abnormality, intracardiac masses, such as thrombi and tumors or endocarditic vegetations. It is also helpful in detection of congenital heart diseases.

M-mod echocardiography

This type of echocardiography is particularly useful for the measurement of sizes of chambers of heart, calculation of ejection fraction and accurate timing of cardiac events such as opening and closing of valves.

Doppler echocardiography

Doppler echocardiography is valuable in detecting abnormal directions of blood flow e.g. aortic or mitral regurgitation and estimation of pressure gradient e.g. gradient across a stenosed aortic valve. There are three modes of Doppler echocardiography:

1. Pulse - wave Doppler (PW)
2. Continuous -wave Doppler (CW)
3. Color Doppler

Experience sharing: a good echo machine should have all three components;

1. Two-dimensional real time echocardiography.
2. M-mod echocardiography
3. Doppler echocardiography

Machines available in market have price ranging from Rs. 10,00000 to 100,00000 and echo charges are usually Rs.1000 to 2500 in Karachi. Low priced machines do not have Doppler. Much of the echo results are operator dependent, therefore when you are referring the patient for echo you must know how well-skilled is the operator in performing echo.

Trans-Esophageal Echocardiography (TEE)

In this technique an ultrasound probe, in the shape of endoscope is passed into the esophagus and positioned behind the heart. It is very helpful in detecting:

- Very small vegetations not detected on transthroacic (usually performed) echocardiogram.
- Thrombus in left atrium or atrial appendage in patients of mitral stenosis and atrial fibrillation.
- .ASD not detected by transthoracic echocardiography.

Stress Echo

In stress echocardiography echo is done during exercise or just after the exercise, or after pharmacological stress by administration of dobutamine, adenosine or dipyridamol. Dobutamine Stress Test (DSE) is now commonly performed to detect stress induced segmental wall motion abnormalities (an indicator of ischemia).

Contrast Echo

Intravenous contrast agents or agitated saline are used intravenously to assess intramyocardial flow pattern; very helpful in detection and to see the direction of flow in shunts such as ASD, VSD (left to right or right to left).

AMBULATORY ECG (Holter monitoring)

This equipment is a battery powered cassette tape recorder which is used for continuous recording of one or more ECG leads for 24 hours. This technique is useful in detecting transient episodes of arrhythmia or ischemia which seldom occur during the short time taken for routine 12-lead ECG recording. Brief paroxysm of tachycardia, an occasional pause in rhythm or intermittent ST segment changes may be identified.

Cardiomemo: It is also an event recorder that is used to record less frequent arrhythmias. Patient is provided with a pocket - sized device that can record and store a short segment of ECG.

RADIONUCLIDE SCANNING (Nuclear imaging)

Thallium 201 scanning

Thallium 201 scanning when injected provides information regarding infarction and non-infarction myocardium.

- Fixed defect in perfusion shows myocardial infarction while the reversible defect indicates myocardial ischemia.
- Initially the radioisotope is injected during exercise, scanning defects indicate zones of ischemia or hypoperfusion if the myocardium is viable (i.e. no infarction).
- Now the scan is performed later during rest, filling of these defects indicates a reversible ischemia and if the defects persist even at rest it means these are infracted areas. Scan charges are about Rs. 3000. Higher rates in private sector.

Technetium -99- labeled sestamibi can be used instead of thallium if viability of myocardium is to be determined.

Indications

Thallium scanning is indicated:

- When resting ECG makes an exercise ECG difficult to interpret (e.g. due to LBBB).
- In patients to detect myocardial infarction in whom exercise testing (ETT) is not diagnostic (e.g. positive test in asymptomatic patients), or is not allowed e.g. in bundle branch block, left ventricular hypertrophy or patient taking digitalis.
- To localize the region of ischemia.
- To distinguish ischemic from infracted myocardium.

MUGA SCAN (Blood pool scanning)

This isotope is injected IV that mixes with circulating blood. The gamma camera detects the amount of isotope-emitting blood in the heart at different phases of cardiac cycle e.g systole and diastole.

Clinical uses

- MUGA Scan is used for detection of ventricular aneurysm
- Left and right ventricular ejection fraction can be measured accurately. Ejection fraction indicates ventricular function.

CARDIAC CATHETERIZATION

Cardiac catheterization is the introduction of a catheter into the circulation.

- Right heart is catheterized by introducing the catheter into a peripheral vein (usually the right femoral vein) and advancing it to the right atrium and right ventricle into the pulmonary artery. The pressures in the right heart chambers and pulmonary artery can be measured directly.
- Left heart catheterization is usually performed via the right femoral artery, catheter enters the left ventricle where pressures are obtained, dye is injected for ventriculography to assess left ventricular function. Coronary angiography is performed by using especially designed right and left coronary artery catheters.

During cardiac catheterization blood samples are withdrawn to measure concentration of ischemic metabolites (e.g lactate) and oxygen to quantify intracardiac shunts.

This invasive procedure by using catheter gives the following information.

- Measurement of pressure in different chambers of heart.
- Blood oxygen content or saturation in different chambers.
- Measurement of cardiac output.

Clinical Uses

1. Identification of coronary artery disease and assessment of its extent. Coronary spasm and thrombosis.
2. Left ventricular dysfunction and ischemic mitral regurgitation.
3. Angiography and angioplasty for acute coronary syndrome.
4. To rule out ischemic cause of cardiomyopathy.
5. To differentiate restrictive cardiomyopathy from constrictive pericarditis.
6. To assess extent and severity of valve disease
7. For assessment of left and right ventricular function (abnormality such as heart failure).
8. It detects atrial and ventricular septal defects.
9. It is performed before surgical correction of congenital heart disease.

CORONARY ANGIOGRAPHY

Coronary angiography is performed during cardiac catheterization. It is the visualization by x-ray contrast material (dye) injected into the arteries. Coronary angiography is performed by introduction of catheter from femoral artery, which is guided under radiological control (fluoroscope) to the left and right coronary arteries and left ventricle. Contrast medium is injected while video images of the recordings are made (on CD).

Clinical uses

It detects and estimates the severity of coronary artery stenosis, therefore revascularization can be performed with by-pass operation or angioplasty.

Indications

Angiography is very commonly performed procedure now a days. Medical students and doctors of other specialties must know the proper indications of angiography therefore they can guide and counsel their patients confidently. Indications are given below according to the clinical situations.

1. **Asymptomatic patient**: evidence of high risk on noninvasive testing (ECG, ETT, Thallium scan, Echo).
2. **Nonspecific or atypical chest pain:** diagnosis of ischemic heart disease is made confidently in majority of patients with non –invasive testing. Angiography should be performed only if there are high- risk findings on noninvasive testing.
3. **Stable angina:** evidence of high risk on noninvasive testing or pain not relieved by medical treatment.
4. **Unstable angina**: high or moderate risk patients refractory to initial adequate medical treatment or recurrent symptoms after initial stabilization.
5. **After angioplasty:** suspected abrupt closure or subacute stent thrombosis after angioplasty or recurrent angina or high risk criteria on non-invasive testing within 9 months of angioplasty and 12 months of bypass operation.
6. **After myocardial infarction:** as an alternative to thrombolytic therapy within 12 hours of onset of symptoms.
7. **Perioperative evaluation before non-cardiac surgery** in patients with suspected or known coronary artery disease.
8. **Before valve surgery** in adults to rule out coronary artery disease, as the bypass grafting is possible in the same operation.
9. **Heart failure:** patients with heart failure having angina or evidence of ischemia on noninvasive testing.

CARDIAC FAILURE

Inability of the heart to maintain adequate cardiac output to meet the demands of the body is known as cardiac failure. It can result from any structural or functional cardiac disorder.

ETIOLOGY

LEFT VENTRICULAR FAILURE

Volume overload

- Aortic regurgitation
- Mitral regurgitation
- Patent ductus arteriosus

Pressure overload

- Systemic hypertension
- Aortic stenosis

Myocardial diseases

- Ischemic heart disease
- Dilated cardiomyopathy
  - Idiopathic (most common)
  - Myocarditis
  - Peripartum cardiomyopathy
  - Diabetes mellitus
  - Hemachromatosis
  - Sarcoidosis
  - Scleroderma
  - Alcohol
- Restrictive and hypertrophic cardiomyopathy

RIGHT VENTRICULAR FAILURE

Volume overload

- Atrial sepal defect
- Tricuspid regurgitation

Pressure overload

- Pulmonary hypertension
- Pulmonary stenosis

Myocardial diseases

Cardiomyopathy secondary to left ventricular failure.

TYPES OF HEART FAILURE

The heart failure may be classified in several ways.

1. Acute versus chronic heart failure
2. Left versus right and biventricular failure
3. Forward versus backward failure
4. Systolic versus diastolic failure
5. Low output versus high output failure

Acute versus chronic heart failure

Acute heart failure

Heart failure developing suddenly in hours or days in a previously asymptomatic patient is called acute heart failure.

Chronic heart failure:

Heart failure developing gradually is called chronic heart failure. In this type of failure a variety of compensatory changes may take place in early phase to improve cardiac function. These adaptive mechanisms allow the patient to adjust and tolerate not only the anatomic abnormality but also a reduction in cardiac output with less difficulty.

Left versus right & biventricular heart

Left sided heart failure

Left-sided heart failure is characterized by a reduction in effective left ventricular output for a given pulmonary venous or left atrial pressure.

An acute increase in left atrial pressure may cause pulmonary congestion or pulmonary edema, while chronic increase in left atrial pressure leads to reflex pulmonary vasoconstriction which protects the patient from pulmonary edema at the cost of increasing pulmonary hypertension (as a compensatory mechanism).

Causes of left heart failure

- Ischemic heart disease (commonest)
- Systemic hypertension
- Mitral and aortic valve disease
- Cardiomyopathies

Right sided heart failure

Right-sided heart failure is characterized by reduction in right ventricular output for any given right atrial pressure. The increased right atrial pressure is manifested as an increased jugular venous pressure and as hepatic congestion.

Causes of right heart failure

- Secondary to left heart failure (most common)
- Chronic lung disease (causing cor-pulmonale)
- Pulmonary embolism or pulmonary hypertension
- Tricuspid and pulmonary valve disease
- ASD & VSD
- Right ventricular cardiomyopathy

Biventricular or congestive cardiac failure (CCF)

When both sides of heart are involved, features of both right and left heart failure are present. In most of the patient right heart failure is a result of preexisting left heart failure.

Forward versus backward failure

Forward failure

In some patients with cardiac failure predominant problem is an inadequate cardiac output that leads to diminished perfusion of vital organs leading to ischemia of these organs is called forward failure. Ischemia of brain causes mental confusion, ischemia of skeletal muscles leads to weakness, ischemia of kidneys causes sodium and water retention leading to symptoms of heart failure.

Backward failure

In some patients cardiac failure presents mainly with features of damming of blood into venous system such as lung congestion in left heart failure and congestion of liver, spleen and other areas in right heart failure.

Systolic versus diastolic failure

In majority of patients heart failure is due to combined systolic and diastolic dysfunction, however isolated systolic or diastolic dysfunction may be present.

Systolic failure

Heart failure may develop as a result of impaired myocardial contraction (systolic dysfunction). The most common cause of systolic ventricular dysfunction is ischemic heart disease usually after myocardial infarction.The left ventricle is usually dilated and fails to contract normally resulting in symptoms of predominantly forward failure.

Diastolic failure

Heart failure may develop due to poor ventricular filling caused by impaired ventricular relaxation (diastolic dysfunction). The most common cause is left ventricular hypertrophy as a result of hypertension and coronary artery disease. Other causes of diastolic dysfunction are hypertrophic and restrictive cardiomyopathy, diabetes and pericardial disease.

Diastolic failure is common in elderly, women and in patients with history of hypertension. It is a common cause of patient's visit to doctor, patients present with shortness of breath and there is history of hypertension only (usually no history of previous MI).

Low versus high cardiac output failure

Low output failure

Low cardiac out put at rest or during exertion characterizes heart failure caused by common conditions such as congenital, valvular, rheumatic, hypertensive, coronary and cardiomyopathic diseases. Low output failure presents with evidence of systemic vasoconstriction such as cold, paler or cyanotic extremities. Pulse pressure is low.

High cardiac output failure

Conditions that are associated with a very high cardiac output such as anemia, beriberi, Paget's disease of bone and thyrotoxicosis may lead to or precipitate heart failure. The extremities are usually warm, and flushed and pulse pressure is wide or normal. Details of high output failure are given at the end of this section.

CHRONIC HEART FAILURE

Heart failure developing gradually is called chronic heart failure. In this type of failure a variety of compensatory changes may take place in early phase to improve cardiac function. These adaptive mechanisms allow the patient to adjust to and tolerate not only the anatomic abnormality but also a reduction in cardiac output with less difficulty

As the disease progresses these compensatory mechanisms fail to improve cardiac function.

In compensated cardiac failure, patient has impaired cardiac function but the adaptive or compensatory changes prevent the development of overt cardiac failure. These compensatory changes are increased heart rate, hypertrophy of cardiac muscles and dilatation of heart chambers. Acute cardiac failure is uncompensated and therefore more symptomatic because time is required to develop these compensatory changes to develop.

COMPENSATORY OR ADAPTIVE MECHANISMS IN HEART FAILURE

A number of compensatory changes occur in the cardiovascular system in chronic heart failure to maintain adequate blood flow to the vital organs of the body as following:

MECHANISM	ADVANTAGE	DISADVANTAGE IN LONG TERM
Sympathetic stimulation	Increased heart rate (as cardiac output depends on stroke volume and heart rate). Sympathetic stimulation causing increased arterial tone, increased heart rate and increased ventricular contractility.	Increases energy expenditure
Remodeling:	Ventricular hypertrophy and dilatation to maintain adequate blood flow.	Leads to deterioration and death of cardiac cells
Fluid water retention due to stimulation of rennin – angiotensin system	Increases ventricular filling pressure (augment preload)	Causes pulmonary congestion

The clinical features in cardiac failure are based on the two factors:

Reduced cardiac output (forward failure)
This results from decreased heart function. This reduced output leads to diminished filling of arterial tree, resulting in ischemia of the organs.

Damming of blood (backward failure)
Heart becomes fail to pump the whole blood coming to it, resulting in damming of blood back into venous system, organs become congested & their functions are distributed.

In majority of patients there is combination of both factors mentioned above.

FEATURES OF LEFT HEART FAILURE

Symptoms

Mostly symptoms are related to lung due to congestion.

Dyspnea or shortness of breath
Patient presents with shortness of breath with progressively increasing severity as follow:
Exertional dyspnea → orthopnea → paroxysmal nocturnal dyspnea → dyspnea at rest → pulmonary edema. Dyspnea is due to damming of blood resulting in pulmonary venous congestion.

Exertional dyspnea: Exertion leads to increased venous return and relative normal right heart transmits this in pulmonary circulation. In the presence of left heart failure blood is not properly pumped to the systemic circulation, resulting in damming of blood in pulmonary veins, producing pulmonary venous congestion. This congestion stimulates fine nerve endings around the terminal alveoli, which produce a sensation of breathlessness. When exercise is stopped, venous return is diminished, congestion subsides and dyspnea is relieved.

Exercise → increased venous return → poor pumping of heart → congestion in the lung → dyspnea.

Orthopnoea: It means breathlessness on lying flat. It indicates that the heart disease is advanced.
Mechanism: there are two circulatory changes on lying flat.

- Redistribution of fluid occurs from tissues into the plasma. Approximately ½ liter of blood pooled in the leg veins during standing is returned to effective circulation, in this way venous return is increased. The workload on the heart becomes increased which already has poor function, therefore lung congestion and dyspnea develop.
- In upright position, hydrostatic pressure helps in draining the upper lung zones into the left atrium, so that respiration can continue in upper zones even the lower zones of the lung are congested. On lying flat, hydrostatic effect is lost & the whole lung becomes congested, so that the patient becomes breathless.

Paroxysmal nocturnal dyspnea: It means episode of breathlessness at night during sleep. It is a result of pulmonary congestion caused by:

- Redistribution of fluid on lying flat results in increased venous return to already poor functioning heart, causing pulmonary congestion.
- Reduced hydrostatic effect in pulmonary veins, which has function to inhibit congestion of the lung.
- Depression of nervous system during sleep leads to reduced awareness of pulmonary congestion. When the congestion becomes of high degree patient becomes severe breathless.
- During sleep, sympathetic system is also depressed which is responsible for cardiac rate. The reduced heart rate leads to pooling of blood in pulmonary vessels, resulting in pulmonary congestion.

The patient wake up with intense breathlessness, which often produces feeling of suffocation. The patient sits upright and opens window in the hope that the cool fresh air will ease his breathing. Attack subsides spontaneously in about half an hour.

Pulmonary edema
It develops in severe left heart failure & is characterized by:

- Persistent severe breathlessness of sudden onset.
- Profuse sweating, skin becomes cold and cyanosed.
- Expectoration of watery, frothy often blood-stained sputum.

Acute cardiac failure after myocardial infarction, myocarditis and acute valvular regurgitation usually present with pulmonary edema in previously asymptomatic patient.

Symptoms due to reduced cardiac output

Fatigue & weakness due to reduced blood flow to skeletal muscles and the CNS.

Nocturia

Occurs due to excretion of fluid retained during the day and increased renal perfusion in the recumbent position at night.

Chronic cough

Chronic non-productive cough, which is often worst in the recumbent position.

> **Symptoms of Left heart failure**
> 1. Dyspnoea, orthopnoea, paroxysmal nocturnal dyspnea
> 2. Fatigue
> 3. Nocturia
> 4. Chronic non-productive cough

On examination

Inspection:

There may be bulging of precordium due to cardiomegaly. There is usually no cardiomegaly in acute heart failure, diastolic heart failure, constrictive pericarditis and restrictive cardiomyopathy.

Palpation:

Apex beat is displaced and heaving in character, if there is left ventricular hypertrophy.

Auscultation

- Gallop-rhythm: tachycardia with third or fourth heart sound is called gallop-rhythm. (Gallop rhythm is called because of its resemblance to the sounds produced by galloping horse).
- Basal crepitations are heard. Rhonchi may be present due to bronchospasm.
- In case of pulmonary edema medium to loud crepitations are heard all over the lungs.
- Signs of pulmonary hypertension such as loud P2 may be present.
- Systolic murmurs due to functional mitral regurgitation may be present as a result of ventricular and annular dilatation.

General physical examination

- Pallor, coldness of extremities, cyanosis of digits, distension of peripheral veins due to vasoconstriction as a result of increased adrenergic activity .
- Cardiac cachexia: it is the wasting that results from anorexia due to hepatic and intestinal congestion and mesenteric hypoperfusion.
- Pulse: tachycardia, reduced pulse pressure, pulsus alternans may be present.
- BP: diastolic BP may be slightly elevated due to increased adrenergic activity.
- Fever may be present.
- Always examine for features of etiology of heart failure such as hypo-or hyperthyroidism.

> **DIFFERENCE IN CARDIAC AND PULMONARY DYSPNEA**
> - Dyspnea due to pulmonary cause has history of asthma, COPD, tuberculosis and other respiratory disorders while in dyspnea of cardiac origin there is history of angina, MI, hypertension and other cardiac disorders.
> - Dyspnea due to asthma or COPD is usually associated with cough with sputum production.
> - Pulmonary dyspnea usually responds to bronchodilators while cardiac dyspnea usually responds to diuretics and nitrates.
> - Plasma BNP: (B- type natriuretic peptide) is a cardiac neurohormone that is elevated in heart failure but not in pulmonary causes.
> - Pulmonary function tests (PFTs) may be helpful

FEATURES OF RIGHT HEART FAILURE

Symptoms

Tissue congestion: tissue congestion results from inability of the heart to empty properly, showing the following features.

- Cerebral: Headache, insomnia, restlessness
- Pulmonary: Cough, dyspnea
- Portal: Anorexia, nausea & vomiting
- Pain in right hypochondrium due to hepatic congestion which stretches the hepatic capsule. This stretching of hepatic capsule stimulates pain receptors and produces pain.
- Renal: Oliguria and nocturia
- Peripheral edema of feet in ambulatory & sacral edema in bed bound patient.

On Examination

1. Raised JVP – Positive hepato-jugular reflux
2. Tender hepatomegaly – due to congestion
3. Dependent pitting edema: in ambulant patients the edema affects the ankles whereas in bed bound patients it collects around the thigh and sacrum. Massive accumulation of fluid may cause ascites or pleural effusion.
4. Evidence of heart disease:
   - Signs of right ventricular or biventricular cardiomegaly.
   - Right ventricular gallop rhythm
   - Functional tricuspid regurgitation due to right ventricular dilatation.

Important signs of right heart failure

1. Tachycardia
2. Raised JVP
3. Pitting peripheral edema
4. Tender smooth hepatomegaly
5. Ascites & pleural effusion (may be present).

Cardiac cachexia

Cardiac cachexia describes the loss of lean (non-edematous) body mass i-e wasting that occurs in some patients with moderate or severe heart failure. It is associated with morbidity and mortality.

PRECIPITATING OR AGGRAVATING FACTORS OF HEART FAILURE IN PATIENTS WITH PRE- EXISTING HEART DISEASE

- Myocardial ischemia or infarction
- Intercurrent illness (e.g. infection)
- Arrhythmia (e.g. atrial fibrillation)
- Inappropriate reduction of therapy
- Administration of a drug with negative inotropic (e.g. beta-blocker or calcium channel blocker) or fluid retaining properties (e.g. NSAIDs, corticosteroids)
- Pulmonary embolism
- Conditions associated with increased metabolic demand (e.g. pregnancy, thyrotoxicosis, anemia).
- IV fluid overload

FRAMINGHAM CRITERIA FOR DIAGNOSIS OF CCF

One major and two minor criteria are required for the diagnosis of congestive cardiac failure.

Major criteria

- Paroxysmal nocturnal dyspnea
- Neck vein distension
- Crepitations
- Cardiomegaly
- Acute pulmonary edema
- S3 gallop
- Increased venous pressure (>16 cmH2))
- Positive hepatojugular reflux

Minor criteria

- Pedal edema
- Night cough
- Dyspnea on exertion
- Hepatomegaly
- Pleural effusion
- Tachycardia
- Vital capacity reduced by one third from normal.

The greatest volume of air that can be exhaled from the lungs after a maximum inspiration

INVESTIGATIONS

ECG:

ECG may show:

- Right or left ventricular hypertrophy
- Myocardial ischemia or infarction
- Arrhythmia

X-ray chest:

- Hilar congestion
- Bat's wings appearance in acute pulmonary edema (opacities tend to spread in a butterfly manner from the hilum, periphery is usually clear)
- Cardiomegaly
- Evidence of pulmonary hypertension.
- Pleural effusion.
- Pneumonia as a precipitating factor may be evident.

Other investigations

Test	Indications & information obtained
Blood CP:	May show anemia
LFT's:	May be disturbed due to congestion
Urea and creatinine	May be abnormal due to decreased renal perfusion.
Serum electrolytes	Diuretic therapy may cause hypokalemia that may cause arrhythmia. Hyperkalemia limits the use of ACE inhibitors. Hyponatremia is a poor prognostic sign.
Cardiac enzymes:	To detect myocardial infarction; if suspected.
Thyroid function test	To rule out occult thyroid disease.
Myocardial biopsy	To identify the cause of dilated cardiomyopathy but rarely performed.
Serum "B-type" natriuretic peptide **(BNP)**	(Present in ventricles) is elevated when ventricular filling pressures are high. It is quite sensitive (>70%) in patients with symptomatic heart failure but less specific in older patients, women and patients with COPD.
Plasma endothelin - 1 concentration:	Raised level is an independent marker of prognosis.
Resting and stress radionuclide angiography:	For estimation of ejection fraction and wall motion abnormality
ETT:	When myocardial ischemia is suspected cause of left ventricular dysfunction.
Cardiac catheterization:	Left heart catheterization is required when significant valvular disease is to exclude. When the presence and extent of coronary artery disease must be determined.

Echocardiography:

Echocardiography is a very important tool for the diagnosis and cause of heart failure. It may demonstrate:

- Systolic or diastolic impairment of left or right ventricle.
- Valve disease.
- Regional wall motion abnormalities in ischemic heart disease.
- Cardiomyopathy.
- Intracardiac thrombus
- Ejection fraction

MANAGEMENT OF CHRONIC HEART FAILURE

TREATMENT STRATEGY

The treatment of heart failure is logically divided into three components:

1. Correction of underlying cause as ischemia, valvular heart disease.
2. Removal of precipitating cause such as pneumonia, anemia.
3. Control of congestive heart failure.

Correction of reversible underlying cause such as:

- Ischemia
- Thyrotoxicosis
- Hypothyroidism
- Valvular lesions
- High cardiac output states
- Arrhythmias
- Drug induced myocardial depression (e.g. beta blocker, calcium channel blocker).
- Acute myocarditis may respond to corticosteroids and immunosuppressive drugs.
- Treatment of hypertension.
- Treatment of pericardial disease

Removal of precipitating cause such as:

- Infection such as pneumonia
- Myocardial infarction
- Pulmonary or urinary tract infection
- Recurrent pulmonary emboli
- Hypoxemia
- Anemia
- Arrhythmia
- Pregnancy
- Hypertension
- Physical, dietary, fluid, and emotional excess

Control of congestive heart failure state by:

Reduction of cardiac workload

- Physical and emotional rest. Bed-rest for 1-2 weeks in symptomatic cardiac failure.
- Small but frequent meals.
- Weight loss by reducing calories intake in obese patient diminishes the cardiac workload.
- Use of vasodilators.

Control of excessive retention of salt and water

- Decreased intake: Low salt diet.
- Increased excretion: Diuretics.

Enhancement of myocardial contractility

- Use of digitalis
- Use of dopamine and dobutamine

TREATMENT STRATEGY FOR CARDIAC FAILURE

ACE inhibitors

↓

Moderate restriction of sodium and physical activity

↓

Combination of diuretics, vasodilator and digitalis

↓

Further restriction of salt and physical activity

↓

Positive inotropic agent

GENERAL MEASURES

1. **Rest**: Bed rest reduces the demands of the heart, therefore, beneficial. Head of the patient should be proposed up to reduce lung congestion.
2. **Diet**: Low salt diet containing max. 5g salt daily. Good general nutrition, weight reduction for obese.
3. **Smoking**: stop smoking
4. **Exercise:** regular moderate exercise within limits of symptoms
5. **Vaccination:** Influenza and pneumococcal vaccination.

DRUG MANAGEMENT

Diuretics, dilators, digitalis

DIURETICS

- Loop diuretics e.g. Frusemide (Lasix)
- Potassium sparing diuretics e.g. spironolactone (Aldactone)
- Thiazide diuretics e.g. metalazone

They act by promoting the renal excretion of salt and water by blocking tubular reabsorption of sodium and chloride; this salt and water excretion results in reduction of blood and plasma volume. This reduction in blood volume leads to reduced pre-load to the heart with a reduction in ventricular filling pressure and an improvement in pulmonary and systemic congestion.

- Diuretic are the most effective means of providing symptomatic relief to patient with moderate to severe congestive cardiac failure.
- Mild heart failure is generally managed with oral thiazide. Combination with potassium sparing diuretic prevents development of hypokalemia. Thiazide diuretics are ineffective when GFR is below 30ml/min. Spiranolactone (a potassium sparing diuretic) is a specific inhibitor of aldosterone, which is often increased in cardiac failure; therefore it is useful to combine it with thiazide or frusemide.
- In severe heart failure, diuretics of different groups can be combined to increase diuretic effect. Loop diuretic e.g. frusemide is most effective. In acute condition, diuretics should be given I/V because they may not be absorbed adequately due to congestion in the gut. Frusemide is given in the dosage of 20-320 mg daily preferably in two or more divided doses. In severe renal insufficiency, larger doses of frusemide such as 500mg may be required. Patients with refractory edema may respond to combination of frusemide and thiazide such as metolazone. Metolazone maintains its activity even in renal insufficiency.
- **Spironolactone** (Aldactone) is a specific competitive antagonist to aldosterone. Along with its effect of potassium sparing diuretic, it inhibits myocardial remodeling and fibrosis and should be given in severe heart failure. RALES trial shows 30% reduction in mortality

when spironolactone (25mg) was added to conventional treatment.

- Side effects: Excessive diuretic therapy may lead to hyponatraemia, hypokalaemia, pre-renal azotemia, hyperglycemia and hyperuricemia.

VASODILATORS

Vasodilator drugs reduce preload and after load resulting in improvement of cardiac function. The most important vasodilator is ACE inhibitor. Drugs in this group are:

- ACE inhibitors
- Angiotensin II receptor antagonists
- Hydralazine
- Nitrates
- Nesiritide

Angiotensin converting enzyme (ACE) inhibitors

The rennin-angiotensin – aldosterone system is activated early in the course of heart failure and plays an important role in the progression of the disease. Therefore inhibition of this system with angiotensin converting-enzyme (ACE) inhibitors should be considered as a part of the initial therapy of the cardiac failure. All patients of cardiac failure should be on ACE inhibitors if there is no contraindication. Prognosis is markedly improved and development of heart failure is slowed with the use of ACE inhibitors.

Mode of action:

ACE inhibitors prevent conversion of angiotensin I to angiotensin II, there by;

1. Preventing salt and water retention, as angiotensin II stimulates aldosterone that causes salt and water retention.
2. Inhibiting peripheral arterial and venous vasoconstriction
3. Inhibiting activation of sympathetic system. Therefore, they improve cardiac function by reducing the preload and afterload.
4. Combination of a diuretic and an ACE inhibitor has many potential advantages e.g.
   - Diuretics activate rennin-angiotensin system, which is counteracted by ACE inhibitors
   - Diuretics cause loss of K+ while ACE inhibitors preserve it, therefore maintaining K+ level.

Side effects:

- Dry cough (common side effect)
- Skin rashes
- Neutropenia
- Hyperkalemia
- Deterioration of renal function
- Postural hypotension especially after first dose and particularly in patients with hypovolemia or hyponatremia due to prior diuretic therapy.
- Angioedema may develop at any time during the use of these agents. Patient may present with dyspnea due to laryngeal edema; therefore always ask about the use of ACE inhibitors if the patient first time presents with dyspnea.

Precautions:

1. Reduce the dose or stop diuretics 24 hours before starting treatment with ACE inhibitors. Patient should remain supine and under observation.
2. If hypotension occurs, elevate the foot end of the bed and if necessary, give I/V saline.
3. Start drug with a low dose of short acting agent as captropil 6.25 mg (Tab. Capoten 25 mg ¼ daily). Blood pressure should be monitored for the first 2-hours after dosing; if there is no significant hypotension the patient may be sent home on a dosage of 12.5 mg (1/2 tab) three times daily.

ACE INHIBITOR DOSAGE IN HEART FAILURE

Drug	Starting dose	Target dose
Captopril (Tab. Capoten) 25 mg	12.5 mg 8-hourly	50mg 8-hourly
Enalapril (Tab. Renitec) 5mg, 10mg	2.5mg 12-hourly	10mg 12- hourly
Lisinopril (Tab. Zestril) 5, 10, 20 mg	5mg daily	5mg 12- hourly
Ramipril (Tab. Tritace) 1.2 mg, 2.5 mg, 5 mg	2.5mg 12-hourly	5mg 12-hourly

Angiotensin II receptors antagonist (AIIRA)

Renin-angiotensin-aldosterone system can also be inhibited by the use of specific angiotensin II

receptor antagonists. These agents are as effective as ACE inhibitors in the management of cardiac failure. The advantage is that they do not cause cough and skin rash, however it is recommended that until further data is available for the efficacy of angiotensin II receptor antagonist, use ACE inhibitors in all patients unless patient has cough or skin rash. Combination of ACE inhibitor and receptor antagonist may give additional benefit.

- Losartan (Tab. Cozaar 50mg, Tab. Eziday 25mg, 50mg)
- Valsartan (Cap. Diovan 80mg)

Nitrates

- Nitrates are not used routinely in heart failure. Long acting nitrates such as isosorbide nitrate may be given if paroxysmal nocturnal dyspnea is uncontrolled.
- Isosorbide dinitrate 20-80 mg orally three times daily is moderately effective in relieving shortness of breath in mild to moderate cardiac failure by reducing preload but in advanced cardiac failure nitrates are less effective because they have little effect on cardiac output.
- Nitrates are mainly used in acute heart failure, in acute cardiogenic pulmonary edema and in acute decompensation of chronic heart failure. Intravenous nitroglycerine (Isoket) is effective in acute heart failure especially when accompanied by hypertension or myocardial ischemia. Starting dose 10-20 μg/kg/min increasing 10μg/kg/min every 5-10min, Max 200 μg /kg/min.

Hydralazine

Combination of oral hydralazine and oral nitrates is an alternative to ACE inhibitors for the treatment of cardiac failure in patients who do not tolerate ACE inhibitors. However they are less effective than ACE inhibitors. Hydralazine 150-300mg/day and isosorbide dinitrate 80-160mg/day resulted in an increase in left ventricular ejection fraction and lower risk of death from all causes. Major side-effects of hydralazine are gastrointestinal distress, headache, tachycardia, hypotension, and the drug induced SLE.

Nesiritide

This new agent is a recombinant form of human brain natriuretic peptide and is a potent vasodilator that reduces ventricular filling pressure and improves cardiac output. It is used mainly in decompensated heart failure and is more effective than IV nitroglycerine.

Nesiritide 2μg/kg IV bolus then 0.01 μg /kg/min.

DIGITALIS

Indications:

- Digoxin is a positive inotropic agent and is the first line therapy in patients with heart failure associated with atrial fibrallation, otherwise reserved for the treatment of severe heart failure (even with sinus rhythm) that has not responded to treatment with a diuretic and an ACE inhibitor.
- Recent trials show that digoxin neither increased nor decreased total or cardiovascular mortality. Digoxin use causes significant symptomatic improvement, decrease in symptoms, number of hospitalization, significant increase in treadmill exercise time and ejection fraction. However there was no benefit or harm with regard to survival, a reduction in deaths due to progressive heart failure was balanced by an increase in deaths due to ischemia and arrhythmia as a result of digoxin therapy..
- Therefore digoxin should be used for those patients who remain symptomatic on diuretics and ACE inhibitors as well as for heart failure patients who are in atrial fibrillation and require rate control.

Mode of action

Digoxin (a short acting digitalis) acts as a positive inotropic agent (increasing force of cardiac contraction) by competitive inhibition of sodium-potassium AT-pase, which results in high intracellular levels of sodium. The intracellular sodium is exchanged for extracellular calcium. High intracellular levels of calcium ions allow increased binding of contractile proteins actin and myosin, enhancing the force of cardiac contraction.

Dosage

Initial dose: (Digitalization)

Rapid digitalization (duration 24 hours):

Single dose of 0.5 mg IV slowly over 10-20 minutes followed by additional 0.25 mg IV every 6 hour to maximum of 1mg in 24 hours. Initial effect is seen after 30 min and peak effect at 2-3 hours.

Indications

- Acute congestive cardiac failure
- Severe chronic failure
- Supraventricular tachyarrhythmia and fast ventricular rate.

Slow digitalization (duration 1 week):
Single oral dose of 0.5 mg for 3 days followed by maintenance dose (0.15-0.5 mg daily).

Indicated for mild-moderate failure.

Pharmakokinetics

- Digoxin is excreted through kidney and halflife is 36-48 hours; therefore dose is reduced in renal impairement.
- Plasma level of digoxin is increased when there is concomitant use of amiodarone, verapamil, quinidine, therefore dose of digitalis should be reduced to half if these drugs are used.
- Antacids and broad spectrum oral antibiotics decrease the absorption of digoxin.

Digoxin toxicity

It is prone to occur in the elderly and in the patients with renal impairment because it is almost excreted unchanged in urine. Renal impairment causes its accumulation, resulting in serious toxicity. Hypothyroid patients are particularly sensitive to digitalis. In case of renal impairment, digitoxin is preferable because it is metabolized by the liver. The therapeutic to toxic ratio of digoxin is quite narrow; digoxin toxicity is uncommon with serum level below 1.4 ng/ml and is present in > 50% of patients above the level of 3 ng/ml. Usually serum level is above 2 ng/ml when patient presents with toxicity. Recommended trough levels of digoxin are between 0.5 and 1 ng/ml when used for heart failure. Usual precipitating factor for digoxin toxicity is hypokalemia that develops due to concomitant diuretic therapy for failure. Digoxin toxicity is confirmed by reversal of symptoms or cessation of arrhythmias after withdrawal of digoxin therapy for 48 hours.

Extracardiac Manifestations

Following symptoms may precede cardiotoxic effects

- Anorexia, nausea, vomiting and diarrhea
- Drowsiness, headache and insomnia
- Xanthopsia (yellow vision).

Cardiac manifestations

- Sinus node arrest
- Heart block
- Multiple ventricular ectopics
- Ventricular bigeminy (alternate ventricular ectopics).
- Junctional tachycardia.
- Paroxysmal atrial tachycardia with block.
- Ventricular tachycardia
- Ventricular fibrillation

Management

- Stop digoxin
- Check urea, electrolytes and plasma digoxin concentration.
- Correct hypokalemia and / or dehydration
- Correct bradycardia using atropine (0.6 mg i.v.) and / or temporary pacing for complete heart block or symptomatic severe block.
- Treat atrial tachycardia with beta-blocker.
- Treat ventricular tachycardia with lignocaine or phenytoin.
- In overdose, specific anti-digoxin antibodies (Fab- fragments) may be useful for life threatening toxicity. Their half life is shorter than digoxin , therefore repeat administration may be required.

N.B Electrical cardioversion for tachyarrhythmias should be avoided if possible, since digitalis toxicity may predispose to ventricular fibrillation or cardiac standstill. If cannot be avoided, patient should be pretreated with lignocaine and low energy level (10J) should be employed initially.

ROLE OF BETA-BLOCKERS

Although beta-blockers have traditionally been considered contraindicated in cardiac failure, however, there is now strong evidence that these agents have important beneficial effect. First trial was done with non-cardioselective beta-blocker Carvedilol (Dimitone) but later trial with metoprolol (Mepressor) and bisoprolol (Concor) also proved 30-35% reduction in mortality as well as reduced hospitalizations. Benefit was seen in patients with underlying coronary disease and in primary cardiomyopathies. Recent recommendation is that stable patients (defined as having no recent deterioration or evidence of volume overload) with mild to moderate heart

failure should be treated with a beta-blocker unless there is non-cardiac contraindication. This must be done gradually and very carefully because patient may deteriorate initially. Carvedilol is initiated at a dosage of 3.125 mg twice daily, and then may be increased to 12.5 and 25 mg twice daily gradually (Note: be careful when writing a beta blocker to the patient of heart failure because you may see this patient next day in emergency, dying with severe pulmonary edema).

ANTI-ARRHYTHMIC THERAPY

- Patients with moderate to severe heart failure have a high incidence of both symptomatic and asymptomatic arrhythmias. Holter's monitoring reveals that up to 70% of patients have asymptomatic episodes of non-sustained ventricular tachycardia. These arrhythmias indicate a poor prognosis. All patients of heart failure with arrhythmias should be given beta-blockers.
- Empiric anti-arrhythmic therapy has not proved beneficial in patients with asymptomatic ventricular tachycardia. In symptomatic arrhythmias and for control of ventricular rate in atrial fibrillation class III antiarrhythmic drug amiodarone (Cordarone) may be given. Amiodarone has its own side effects related to lung, thyroid, and liver; it is negative inotropic and poorly tolerated by patients with advanced heart failure. Therefore now the choice for symptomatic arrhythmia is catheter based ablation and implantable defibrillator not the antiarrhythmic drugs.
- Cordarone is available in tablet of 200mg, dosage is 200 mg 3-times daily for 1 week, then 200 mg 2-times daily for 1 week and then 200 mg daily.
- Patients with sustained episodes of ventricular tachycardia should receive **implantable cardioverter-defibrillator (ICD).** Use of amiodarone (Cordarone) suppresses PVCs and VT episodes but there is no survival benefit and is not given routinely.

ANTI-ISCHEMIC THERAPY

Relatively prolonged ischemic episodes are associated with significant abnormalities of ventricular function resulting in heart failure; in this condition diuretics, vasodilators and digitalis are not effective but anti-ischemic treatment such as nitrates improve the condition. Elderly patients with myocardial ischemia frequently present with signs and symptoms of heart failure

ANTICOAGULANTS

Patients with severe left ventricular dysfunction are prone to develop systemic arterial emboli, particularly when they are in atrial fibrillation. Therefore prophylactic anticoagulants are prescribed for patients with atrial fibrillation and those with severe dilated cardiomyopathy (ejection fraction < 20%) in normal sinus rhythm.

MANAGEMENT OF DIASTOLIC HEART FAILURE

- Diuretics are mainstay of treatment but caution should be exercised to maintain cardiac output (i.e. diuretics are treatment of choice but do not overuse them).
- ACE inhibitors and spironolactone may be supportive with diuretics but they do not cause ventricular relaxation and are not as effective as in systolic failure

NON- PHARMACOLOGICAL TREATMENT OF HEART FAILURE

CORONARY REVASCULARIZATION

Since underlying coronary artery disease is the cause of heart failure in the majority of patients, coronary revascularization (mostly bypass grafting) may improve symptoms and prevent progression if there is evidence of ischemia.

Hibernating myocardium is a reversible left ventricular dysfunction due to coronary artery disease that responds positively to inotropic stress and indicates the presence of viable heart muscle that may recover after revascularization.

Myocardial stunning is a reversible ventricular dysfunction that persists following an episode of ischemia when blood flow has returned to normal.

BIVENTRICULAR PACING

In patients with heart failure and left bundle branch block and functional class III heart failure, cardiac conduction abnormalities can trigger mechanical dys-synchrony of ventricular contraction impairing cardiac performance. In these patients bivenrtricular pacing in both right and left ventricle produces improvement in symptoms and exercise tolerance.

IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR

Patients with sustained episodes of ventricular tachycardia should receive implantable cardioverter- defibrillator (ICD).

LEFT VENTRICULAR ASSIST DEVICES (LVAD)

These are pump like devices that receive blood and pump with pressure working like ventricles. They are required in severe heart failure when the pumping function of ventricles is severely impaired. These devices are very expensive.

SURGICAL TREATMENT

CARDIAC TRANSPLANTATION

Patient with severe heart failure and limited life expectancy are considered candidates for heart transplantation. One-year survival rate after transplantation exceeds 80-90% and five-year survival rates above 70%.

Indications

- End stage heart disease with poor (6-12 month) prognosis, refractory to medical and surgical therapy.
- Functional class III or IV.
- Age < 60 years.
- Pulmonary vascular resistance < 3 RU.
- Strong self -motivation.

Contraindications

- Malignancy
- Active infection
- Advanced insulin dependent diabetes.
- Kidney and liver dysfunction
- Advanced peripheral vascular disease
- Active alcoholism

Complications

- *Rejection*: causing failure or arrhythmia.
- *Accelerated atherosclerosis* in the coronary arteries of donor. Patient presents with recurrent cardiac failure, angina is rare because heart has been denervated.
- *Infection*

TREATMENT OF HEART FAILURE

1. Diuretics
   - Thiazide Frusemide
   - Spironolacone
2. Vasodilators
   - ACE inhibitors (most useful)
   - Angiotensin – receptor antagonist
   - Nitrates, Hydralazine
3. Digitalis
4. Beta-blockers
5. Anti- ischemic therapy
6. Anticoagulants
7. Coronary revascularization.
8. Implantable cardioverter- defibrillator (ICD)
9. Biventricular pacing
10. Left ventricular assist devices (LVAD)
11. Cardiac transplantation

COMPLICATIONS OF HEART FAILURE

Uremia due to:

- Diuretic therapy
- Low cardiac output
- Treatment with vasodilators or dopamine may improve renal perfusion.

Hypokalemia due to:

- Diuretic therapy
- Hyperaldosteronism (activation of the rennin-angiotensin system and impaired aldosterone metabolism due to hepatic congestion).

Hyponatremia due to:

- Diuretic therapy
- Inappropriate water retention

Impaired liver function due to

- Hepatic congestion and poor hepatic perfusion;
- Abnormal liver function tests, mild jaundice;
- Anticoagulants potentiated

Thrmboembolism due to:

- Deep vein thrombosis and pulmonary embolism (low cardiac output, immobility)
- Systemic emboli (intracardiac thrombus e.g. mitral stenosis)
- LV aneurysm and arrhythmias e.g. atrial fibrillation

Arrhythmias due to:

- Underlying heart disease
- Electrolyte changes (e.g. hypokalemia)
- Increased circulating catecholamines
- Drug effects (e.g. digoxin toxicity)

REFRACTORY HEART FAILURE

When the response to ordinary treatment is inadequate, heart failure is considered to be refractory. Following may be the factors responsible for refractory heart failure:

- An underlying and overlooked cause of heart disease that may be treatable with surgical or medical therapy such as silent aortic or mitral stenosis, infective endocarditis, hypertension or thyrotoxicosis.
- One or combination of the precipitating factors of heart failure, such as pulmonary or urinary tract infection, recurrent pulmonary emboli, hypoxemia, anemia, or arrhythmia.
- Complications of overly vigorous therapy such as digitalis toxicity, hypovolemia, or electrolyte imbalance.

PROGNOSIS

Annual mortality rate is 5% in stable patients with mild symptoms and 30-50% in patients with advanced progressive symptoms.

Poor prognostic factors in heart failure are:

- Left ventricular dysfunction (ejection fraction < 20%).
- Prominent symptoms and limitation of exercise capacity (max. oxygen consumption < 10 ml/kg/min.
- Secondary renal insufficiency.
- Hyponatremia
- Hypokalemia (potassium < 3 mEq/L).
- Poor response to treatment.
- When underlying heart disease is not treatable.

About 50% deaths are due to ventricular arrhythmias and 50% due to pump failure.

Causes of right ventricular hypertrophy

- Mitral stenosis
- Pulmonary stenosis
- Any congenital heart disease with right to left Shunt.
- Chronic lung disease
- Multiple pulmonary emboli

Causes of left ventricular hypertrophy

- High blood pressure
- Aortic stenosis
- Aortic regurgitation
- Mitral regurgitation
- VSD

ACUTE HEART FAILURE

Heart failure developing suddenly in hours or days in a previously asymptomatic patient is called acute heart failure. Patient presents with shortness of breath due to acute pulmonary edema or with cardiogenic shock. It occurs in the following conditions:

- Myocardial infarction in which there is extensive loss of ventricular muscle.
- Complications of MI such as rupture of interventricular septum causing ventricular septal defect (VSD), mitral regurgitation due to rupture of chorda tendenae or papillary muscle.
- Acute valvular regurgitation such as aortic regurgitation in infective endocarditis and or valvoplasty.
- Myocarditis.
- Acute pulmonary embolus causing obstruction of the circulation.

Cardiac temponade: it is also a common condition usually as a complication of viral or tuberculous infection.

CAUSES OF ACUTE VALVE FAILURE

Aortic regurgitation

- Aortic dissection
- Infective endocarditis
- Ruptured sinus of Valsalva

Mitral regurgitation

- Papillary muscle rupture due to acute myocardial infarction
- Infective endocarditis
- Rupture of chordae due to myxomatous degeneration, or blunt chest wall trauma.

Prosthetic valve failure

CLINICAL FEATURES

Acute cardiac failure may present in three ways:

1. Acute cardiogenic pulmonary edema
2. Cardiogenic shock
3. Acute decompensation of chronic heart failure

ACUTE CARDIOGENIC PULMONARY EDEMA

An increase in the fluid content of the extravascular tissues of the lung is known as pulmonary edema. It is a life-threatening emergency characterized by extreme breathlessness.

Etiology

Left sided heart failure is the cause of pulmonary edema that may result from:

- Left ventricular systolic or diastolic dysfunction as in myocardial infarction.
- Left atrial outflow obstruction as in mitral stenosis.
- Left ventricular outflow obstruction as in aortic stenosis, hypertrophic cardiomyopathy.
- Left ventricular volume overload as in mitral and aortic regurgitation.

Pathogenesis

In left sided failure there is increase in pulmonary capillary pressure. The high pulmonary capillary pressure causes increased filtration of fluid out of the capillaries into the interstitial space (interstitial edema). Further accumulation of fluid disrupts intercellular membrane leading to collection of fluid in the alveolar spaces (alveolar edema) resulting in decreased diffusing capacity, hypoxemia and shortness of breath.

Clinical features

Onset – Sudden

Respiratory features

- Severe acute breathlessness
- Wheezing
- Productive cough with blood tinged – (pink), copious frothy sputum ("cough, cough, cough spit, spit, spit").
- Rapid breathing with use of accessory muscles.
- Crepitations and rhonchi are heard throughout the chest.
- Patient sits upright or stand exhibiting air hunger.
- Sweating is profuse, skin is cold and cyanotic reflecting low cardiac output and increased sympathetic activity.
- Patient is extremely anxious and there is feeling of drowning.

Cardiovascular features

- Tachycardia
- Raised JVP (in biventricular failure)
- Cardiac auscultation is difficult due to respiratory sounds however gallop rhythm and loud P2 may be audible.
- Blood pressure is elevated above the patient's baseline (unless cardiogenic shock is present) due to vasoconstriction due to increased sympathetic activity.

Investigation

ECG

ECG may be abnormal according to the cause:

- Ischemia or MI
- Left ventricular hypertrophy with strain pattern in hypertension.

X-ray chest:

- Diffuse haziness due to alveolar fluid and
- Kerley's B lines of interstitial edema

Arterial blood gases:

- Initially PaO2 and PaCO2 fall, later PaCO2 increases.

Elevated pulmonary capillary wedge pressure

Usually above 20 mmHg.

MANAGEMENT

1. The patient should be placed in a *sitting* position with legs dangling over the side of the bed; this facilitates respiration and reduces venous return. Pulse oximeter should be connected to see oxygen saturation.

2. *High concentration oxygen* by mask to keep Po2 greater than 60 mmHg.
   Noninvasive pressure support ventilation may improve oxygenation and prevents CO2 retention.
   If respiratory distress remains severe, endotracheal intubation and mechanical ventilation may be necessary.

3. *Morphine* (4-8 mg I/V) plus an antiemetic metoclopromide (Maxolon 10 mg I/V) because morphine induces vomiting. It may be repeated after 2-4 hours Morphine decreases anxiety and increases venous capacitance leading to lowering of left atrial pressure. (i.e. decreasing pre-load) that results in alleviation of breathlessness.
   N.B. Morphine must be avoided if the systolic B.P. is less than 90 mm Hg.

4. *Diuretics:* Inj. Lasix 40-80 mg I/V produces immediate vasodilatation (due to its direct

action in addition to more delayed diuretic function).

5. *Vasodilators* e.g. nitroglycerine (Isoket) infusion produces prompt relief by reducing the preload.
6. *Nebulization with salbutamol* nebulization with Ventolin may be required because bronchospasm may occur in response to pulmonary edema that may itself exacerbate hypoxemia and dyspnea. Aminophylline may be used for bronchospasm. *Aminophylline* 250 mg diluted in 10cc of distill water is infused over 20 minutes. (Rapidly given amionphylline precipitates cardiac arrhythmia) It produces bronchodilatation, vasodilatation and increased cardiac contraction in severe heart failure).
7. *Inotropic agents* may be required in low output states particularly when hypotension is present. Dobutamin (Dobutrex) 2-10 micro gm/kg/min by infusion improves cardiac contraction in severe heart failure).

CARDIOGENIC SHOCK

Cardiogenic shock (pump failure) is the most severe clinical expression of left ventricular failure and is associated with extensive damage to left ventricular myocardium.

Causes

- Myocardial infarction (most common)
- Mechanical complications of MI such as free wall rupture, VSD, papillary muscle rupture (causing mitral regurgitation).
- Right ventricular infarction

Cardiogenic shock is a severe failure of tissue perfusion usually characterized by hyotension (Systolic B.P. below 80 mm Hg) and signs of hypoperfusion such as

- Cold and clammy skin
- Cyanosis
- Oliguria or anuria
- Altered mental function – anxiety, confusion and fatigue.

The shock is caused by infarction of large area of left ventricle (approximately 40%). These patients usually have severe coronary artery disease. Oxygen delivery is insufficient to maintain aerobic metabolism therefore lactic acidosis is a metabolic consequence. Mortality ranges 70-100%.

It should be differentiated from non-cardiogenic shock by measuring the pulmonary capillary wedge pressure, which will be low in conditions where the vascular capacity has expanded (i.e. vasodilatation) e.g. in septicemia, or the circulatory fluid volume has decreased (i.e. hypovolemia). The pulmonary capillary wedge pressure will be normal or elevated in cardiogenic shock.

INVESTIGATIONS

ECG

- Evidence of old and new infarction.
- Right ventricular infarction accompanying inferior wall MI diagnosed on right-sided chest leads especially V4.
- Arrhythmias.

Chest x-ray

- Cardiomegaly and pulmonary congestion.
- No cardiomegaly in acute infarction.

Echocardiography

Assessment of right and left ventricular function, valvular function, detection of shunt (ASD, VSD), pericardial fluid and temponade.

Monitoring of pulmonary capillary wedge pressure (PCWP)

Monitoring of pulmonary capillary wedge pressure (PCWP) by Swan-Genz catheter is helpful in establishing the diagnosis and cause of cardiogenic shock and planning and monitoring the therapy. In patient of cardiogenic shock due to left ventricular failure PCWP is elevated while in right ventricular failure or hypovolemia it is low.

MANAGEMENT

Following options may be used for cardiogenic shock:

- Inotropic support: dopamine and dobutamine, noradrenaline.
- Intraaortic balloon counterpulsations.
- Thrombolysis
- Early revascularization by angioplasty or bypass surgery (most important).
- Mechanical complications such as VSD and mitral regurgitation requires urgent surgery.

Right ventricular (RV) infarction

IV fluids are required in RV infarction to increase right ventricular preload and output. Inotropes are required if shock persists, despite adequate fluid administration.

Arrhythmias

- VT or SVT: cardioversion.
- Bradyarrhythmias: atropine and pacemaker.

Mechanical ventilation and oxygen required in majority of cases.

Intra-aortic balloon pump (IABP)

It is the mechanical device that assists the left ventricle. The IABP is placed in descending aorta through femoral artery. The balloon inflates during diastole to increase diastolic pressure greater than systolic pressure to improve coronary perfusion. The balloon deflates at the end of diastole immediately before left ventricular contraction, abruptly decreasing the afterload and improving left ventricular ejection fraction.

IABP is indicated in shock due to severe ischemia, severe left ventricular failure, acute MR or VSD (used as a bridge to intervention).

Revascularization

Revascularization is the only definitive therapy shown to decrease mortality in patients who develop cardiogenic shock following myocardial infarction. Angioplasty or bypass surgery improves survival; 60-80% in patients with revascularization while 0-30% in patients without intervention.

Thrombolytic therapy is less successful in patients with cardiogenic shock due to low flow state, however it should be given to patients with MI and cardiogenic shock if patient is not candidate for angioplasty or bypass surgery (CABG) or if immediate revascularization (primary intervention) is not available, as in majority of cases in Pakistan.

SPECIAL FORMS OF HEART FAILURE

HIGH CARDIAC OUTPUT FAILURE

Conditions that are associated with a very high cardiac output by themselves are rarely responsible for heart failure, but their development in the presence of heart disease often precipitates heart failure. In these conditions increased requirement of the peripheral tissue for oxygen can be met only by an increase in cardiac output, normal heart can compensate it by increasing cardiac output but the diseased heart or normal heart for a prolonged period is unable to compensate, resulting in heart failure.

Causes

- Anemia
- Congenital or acquired arteriovenous fistula
- Thyrotoxicosis
- Beriberi heart disease
- Paget's disease of bones
- Fibrous dysplasia
- Multiple myeloma
- Polycythemia vera
- Carcinoid syndrome
- Acromegaly
- Pregnancy

Arterial pulses are of high volume (bounding pulse).

Management

Anemia:

- Give packed red cells slowly 250-500 ml in 24- hours with frusemide (Lasix) 40 mg IV every 8-12 hours. Monitor for shortness of breath and basal crepts.
- Iron, folic acid and B12.
- Diuretics and digoxin are given in cardiac failure while the ACE inhibitors are not helpful because peripheral resistance is already markedly reduced.

Beriberi: Thiamine along with digoxin and diuretics.

Paget's disease of bones: bisphosphonate or calcitonin along with digoxin and diuretics.

PERIPARTUM CARDIOMYOPATHY

Cardiac failure that develops during pregnancy (usually in last month) or during the first 6 months after delivery in a woman without a history of heart disease and with no other cause is termed peripartum cardiomyopathy.

Incidence: 1:4000 to 1:1000, highest in Africa. More often in older women, those with twins, and in patients with pregnancy induced hypertension.

Etiology: unknown, may be immune or viral.
Symptoms: features of CCF
Course: course of the disease is variable; many cases improve or resolve completely over several months, but others progress to refractory heart failure. In patients who continue to have symptoms and signs of the disease for more than 6 months after delivery, the mortality rate is high and the subsequent pregnancy is especially dangerous.

ECG: tachycardia, atrial or ventricular arrhythmia may be present.
Echo: dilated heart chambers, mural thrombi may be present (source of pulmonary and systemic emboli).

Management

- Treatment of heart failure.
- Anticoagulation, if echo shows mural thrombi.

Prognosis

- If the cardiomegaly does not resolve in 6 months after the onset of symptoms, 5 year mortality rate is 35%. If it is resolved then mortality rate is still about 15%.
- If cardiomegaly does not resolve and another pregnancy intervenes, cardiomyopathy recurs in 50% of cases with an almost 100% mortality rate.

SYSTEMIC HYPERTENSION

Sustained high blood pressure is known as hypertension. Blood pressure 140/90, at least two readings on separate occasion is considered hypertension. Hypertension is classified according to the recommendations of seventh Joint National Committee (JNC-7)

Classification of blood pressure measurements according to JNC-7

Category	Systolic Blood Pressure (mm Hg)	Diastolic Blood Pressure (mm Hg)
Optimal	<120	< 80
Normal	< 130	< 85
Pre-hypertension	130-139	85-89
Hypertension Stage 1 (mild)	140-159	90-99
Stage 2 (moderate)	160-179	100-109
Stage 3 (severe)	> 180	>110

Even borderline hypertension (prehypertension) may cause significant rise in stroke and cardiovascular deaths.

ETIOLOGY

Primary (Essential) hypertension

In about 95% of cases no cause of hypertension can be identified, and this form of hypertension is called primary or essential hypertension. The onset of essential hypertension is usually between ages 25 and 55 years; it is uncommon before age 20.

Secondary hypertension

In about 5% of cases, cause of hypertension can be discovered. This form is called secondary hypertension. Most of the patients are young and cause of hypertension is usually renal failure, renal artery stenosis, or coarctation of aorta. Secondary hypertension is more likely and investigations

should be performed to rule out secondary causes in the following patients:

- Onset of hypertension below age 20 or after 50 years.
- Patients with clinical or biochemical features of specific disorder.
- Patients who have previously controlled hypertension but now become refractory to treatment.
- Accelerated hypertension.

ESSENTIAL HYPERTENSION

Precipitating factors

- Genetic factors: children of hypertensive patients are more prone to develop hypertension.
- Obesity, lack of exercise
- Heavy alcohol intake
- Excessive salt intake
- Cigarette smoking
- Polycythemia
- NSAIDs increase blood pressure about 5mmHg
- Low potassium intake
- Sympathetic over activity
- Insulin resistance

Pathogenesis

Exact mechanism unknown. Following are the suggestions.

B.P = Cardiac output X Peripheral resistance

In the beginning of essential hypertension, the increase of blood pressure is due to a small increase in cardiac output. This could be due to sympathetic overactivity. Later in the disease, the cardiac output induces vascular changes (increased peripheral resistance) that increase the blood pressure.

SECONDARY HYPERTENSION

Causes of secondary hypertension

Renal disease

- Renal vascular disease
- Parenchymal renal disease, particularly glomerulonephritis
- Polycystic kidney disease

Endocrine disease

- Pheochromocytoma
- Cushing's syndrome
- Primary hyperaldosteronism (Conn's syndrome)
- Hyperparathyroidism
- Acromegaly
- Primary hypothyroidism
- Thyrotoxicosis
- Congenital adrenal hyperplasia due to 11-β-hydroxylase, or 17-hydroxylase deficiency
- 11-β hydroxysteroid dehydrogenase deficiency

Drugs

- Oral contraceptives containing estrogens, anabolic steroids, corticosteroids, non-steroidal anti-inflammatory drugs, sympathomimetic agents.

Alcohol, coarctation of aorta and pregnancy (pre-eclampsia)

- ***Renal vascular disease*** (renal artery stenosis) results from fibromuscular dysplasia in young people and due to atheroma of renal artery in elderly. Renal vascular disease should be suspected 1) if the onset of hypertension below age 20 and after 50 years. 2) if there are epigastric or renal artery bruit. 3) if there is atherosclerotic disease of aorta or peripheral arteries. 4) if there is abrupt deterioration of renal function after administration of ACE inhibitors (in case of bilateral renal artery stenosis).

  Renal causes of hypertension are often associated with sodium and water retention, and in many cases with high plasma concentrations of rennin. Renin causes the production of potent vasoconstrictor agent angiotensin II that stimulates aldosterone secretion (secondary hyperaldosteronism) and thus causes sodium retention. This salt and water retention produces hypertension.
- ***Conn's syndrome*** (primary aldosteronism) is associated with sodium retention. In this condition only serum aldosterone is high while in secondary hyperaldosteronism serum aldosterone and rennin both are raised.
- Long standing hypertension cause thickening of walls of small arteries and development of atheroma in large arteries, therefore increasing peripheral vascular resistance. It causes further rise in blood pressure.

CLINICAL FEATURES

Symptoms

1. Mostly asymptomatic discovered on routine examination or when a complication occurs.
2. Suboccipital pulsating headache, characteristically occurring early in the morning and subsiding during the day is characteristic, but any type of headache may occur.
3. Accelerated hypertension is associated with somnolence, confusion, visual disturbances, nausea and vomiting (called hypertensive encephalopathy).
4. Symptoms of secondary causes of hypertension if present. For example pheocromocytoma may present with episodic hypertension along with anxiety, palpitation, profuse perspiration, pallor, tremor and nausea and vomiting.
5. Symptoms of complications such as heart failure, stroke, renal failure etc.

Signs

1. In majority of patients, high blood pressure may be the only sign, but in others, features of cause of hypertension may be noted e.g. abdominal bruit – due to reno-vascular obstruction, delayed femoral pulses – due to coarctation of aorta.

2. Features of complications such as hypertensive heart disease; the disease produced by the secondary effects on the heart of prolonged sustained systemic hypertension e.g. left ventricular hypertrophy presents with:
   - Prominent left ventricular apical heave.
   - Loud aortic second heart sound.
   - Fourth heart sound.

COMPLICATIONS OF HYPERTENSION

The adverse effects of hypertension principally involve the CNS, retina, heart and kidneys.

CNS

- **Stroke:** It results from cerebral hemorrhage or infarction mostly as a complication of hypertension.
- **Hypertensive encephalopathy:** It is characterized by severe hypertension with neurological symptoms e.g. transient disturbance of speech or vision, disorientation, fits and unconsciousness.
- **Subarachnoid hemorrhage:** It is also more common in hypertensive patients.
- **Multi-infarct dementia.**

RETINA

Retinal changes are graded as following:

- **Grade 1:** tortuosity of the retinal arteries with increased reflectiveness (silver wiring).
- **Grade II:** Grade I plus appearance of arteriovenous nipping produced when thickened retinal arteries pass over the retinal vein.
- **Grade III:** grade II plus flame-shaped hemorrhages and soft "cotton wool" exudates due to small infarcts.
- **Grade IV:** Grade III plus papilledema (blurring of the margins of the optic disc).

HEART

- Left ventricular hypertrophy and ultimately left ventricular failure.
- Ischemic heart disease.
- Aortic dissection

KIDNEYS

Long standing hypertension may cause nephrosclerosis (hypertensive nephropathy) that

> **COMPLICATIONS OF HYPERTENSION**
>
> **Heart**
> - Left ventricular hypertrophy and then failure
> - Ischemic heart disease
>
> **CNS**
> - Stroke
> - Hypertensive encephalopathy
> - Subarachnoid hemorrhage
>
> **Retina**
> Grade 1 → Grade IV changes
>
> **Kidney**
> Proteinuria and progressive renal failure

EXAMINATION OF HYPERTENSIVE PATIENT

General inspection

- Look for evidence of associated diseases such as: round face and truncal obesity of Cushing's syndrome.
- Muscular development in upper extremities more than lower extremities suggesting coarctation of aorta.
- Acromegaly, polycythemia and uremia.

Pulse

Feel radial pulse and examine for radiofemoral delay and radioardial asymmetry.

Blood pressure

Take blood pressure, with patient lying and standing. A rise in diastolic blood pressure on standing occurs typically in essential hypertension; a fall in BP on standing may suggest a secondary cause.

Face

Inspect conjunctiva for congestion (polycythemia).

Examination of fundi (very important)

Examine for the hypertensive changes (retinopathy).

Examination of precordium

- Prominent left ventricular apical heave
- Loud aortic second heart sound
- Fourth heart sound.

Auscultation of lung

Auscultate for basal crepts (for heart failure)

Abdomen (very important for postgraduate exams)

- Palpate for renal or adrenal masses such as polycystic kidney and adrenal tumor and for aortic aneutrysm
- Auscultate for renal bruit.

Other signs

- Measurement of BP in lower extremities if hypertension develop before the age of 30 years (for coarctation of aorta).
- Look for the other signs such as signs of previous stroke.
- Pedal edema

Check report of urine analysis

INVESTIGATIONS

Investigations for initial evaluation of hypertension performed in all patients are as following:

Urine analysis

Urine analysis for proteinuria, hematuria and casts; signifying primary renal disease or nephrosclerosis.

Hematocrit

To detect polycythemia

Serum urea and creatinine

Renal failure may be the cause or consequence of hypertension.

Serum potassium

Low serum potassium is typical of hyperaldosteronism.

Fasting blood sugar

To detect hyperglycemia, as diabetes mellitus is another risk factor for artherosclerotic heart diseases.

Lipid profile

Dyslipidemia is another risk factor for atherosclerosis.

Serum uric acid

Because hyperuricemia is a relative contraindication of diuretic therapy.

ECG

ECG may show left ventricular hypertrophy and strain pattern.

Investigations that may be added:

Chest x-ray

Look for cardiomegaly and heart failure, however it is not the routine investigation and should be performed if the complication of hypertension is suspected.

Echocardiography

It should be performed in patients with clinical symptoms or signs of cardiac disease.

Special investigations to screen for secondary hypertension:

- Renovascular disease: radioisotope scan, renal duplex ultrasound, and angiography.
- Pheochromocytoma: 24-h urinary catecholamines.
- Cushing's syndrome: overnight dexamethasone suppression test or 24-h urinary cortisol

> **SYSTOLIC VERSUS DIASTOLIC HYPERTENSION**
>
> Until recently, hypertension was diagnosed and categorized primarily based upon diagnostic blood pressure reading. However, it is recognized that morbidity and mortality increases as both systolic and diastolic blood pressure rise, and that in individuals over age 50 the systolic B.P is better predictor of complications. Therefore hypertension is now diagnosed based upon elevation of either systolic or diastolic blood pressure.

MANAGEMENT OF HYPERTENSION

Who should be treated?

Patient with mild hypertension without other cardiac risk factor should be treated non-pharmacologically with modification of life-style such as regular exercise, low salt intake and weight reduction while the patient with major risk factor such as diabetes or heart failure should be treated with antihypertensive therapy even their blood pressure is in the high normal range.

GENERAL MEASURES

1. Weight reduction
2. Reduction in alcohol consumption
3. Stop smoking to reduce the risk of coronary vascular disease
4. Salt restriction – moderate salt restriction helps in lowering the B.P. Patient is advised not to add salt at the table. Strictly salt restriction is unnecessary.
5. Avoid stress.

DRUG THERAPY

Antihypertensive drug therapy is usually started with single drug initially with small doses and then gradually to usual doses, but if there is incomplete response a second drug is added.

Single drug treatment:

One of the following drugs can be used

- Thiazide diuretics
- Beta blockers
- ACE inhibitors
- Calcium channel blocker
- Alpha blocker

Combination therapy

Most patients with hypertension can be controlled with single agent. If single drug treatment is unsuccessful, then the combination therapy may be given as two-drugs or triple-drug therapy.

Two-drug therapy

1. Diuretic + beta-blocker + Calcium channel blocker or vasodilator.
2. Diuretic + ACE inhibitor + calcium channel blocker or beta-blocker
3. Calcium channel blocker + ACE inhibitor + beta blocker.

Blood pressure stage	Group A No risk factor, no end organ damage	Group B One risk factor not including diabetes, not end organ damage	Group C Diabetes and / or end organ damage
Prehypertension 130-139/ 85-89	Lifestyle modification	Lifestyle modification	Drugs therapy
Stage 1 (140-159/ 80-99)	Lifestyle modification *up to 12 month).	Lifestyle modification (up to 6 month)	Drug therapy
Stage 2 and 3 (> 160 / > 100)	Drug therapy	Drug therapy	Drug therapy

ANTI-HYPERTENSIVE DRUGS

DIURETICS

Mechanism of action

1. Decreasing plasma volume via renal excretion of sodium and water, therefore reducing cardiac output.
2. Reduction of peripheral vascular resistance.

Advantages

- They are more effective in older individuals, obese, blacks, with CHF or chronic renal failure.
- Relatively more effective in smokers than in non-smokers.
- Most effective agent to reduce systolic hypertension.
- Inexpensive, once per day dosing.
- Diuretics alone control hypertension in 50% of cases.

Side effects

1. Metabolic
    - Hypokalemia, hyponatremia
    - Hyperglycemia, hypercholesterolemia,
2. Impotence, skin rash and muscle cramp
3. Ototoxicity by loop diuretics with IV dosing
4. Gynaecomastia in men and breast tenderness in woman – by spironolactone.

Thiazide diuretics

They are the most widely antihypertensive because the duration of action is longer, diuresis is not so severe and inexpensive.

- Hydrochlorothiazide (Aldactazide) one tablet daily.

Loop Diuretics

They are more potent but their use in hypertension is restricted to those with cardiac or renal failure.

- Frusemide (Lasix) 40 mg daily.

Potassium sparing diuretics

They are not effective antihypertensive when used alone therefore combined with other diuretic to prevent hypokalemia. Amiloride and traimterene.

- Moduretic: Combination of hydrochlorothiazide and K + sparing amiloride.

BETA – BLOCKERS

Mechanism of action

They are effective in hypertension because they decrease the heart rate and cardiac output by competitive inhibition of the effects of catecholamine at beta-adrenergic receptors. They also inhibit rennin. Beta-blockers are effective as single therapy in about 50% of cases of hypertension.

Types of beta – blockers

Cardioselective beta-blockers

They are relatively specific to the cardiac beta-1 receptors in low doses but in high doses they do not remain cardioselective and block beta – 2 receptors that are also located in the bronchi and vasculature. (Blockage of beta-2 receptor causes bronchospasm, cold extremities).

Dug	Initial dose	Dosage range
Atenolol (Tenormin)	25mg once daily	200-1200 in 1 or 2 doses
Metoprolol (Lopressor)	50mg in 1-2 doses	50-200mg in 1-2 doses
Bisoprolol (Concor)	5mg once daily	2.5-10mg once daily

Non cardioselective beta-blockers

They block both beta-1 and beta-2 receptors therefore along with decreasing heart rate and cardiac output they also cause bronchospasm and cold extremities.

- Propranolol (Inderal), timolol and nadolol are non-selective beta-bockers.
- Labelalol blocks alpha and beta both types of receptors.

Advantages of beta blockers

- Ideal in hypertensive patients with angina or previous myocardial infarction.
- Favored in young and in patients with migraine.

Side effects

- Fatigue, and impotence
- Insomnia, depression and nasal congestion (more common with propranolol).

- Adverse effects on lipid profile: increased triglyceride and decreased HDL.
- Deterioration of CHF, bronchospasm, hyperglycemia and peripheral vascular disease
- Abrupt withdrawal can precipitate angina.
- Heart block is also a common complication; therefore monitor pulse for bradycardia.

CALCIUM CHANNEL ANTAGONISTS

Mode of action

They decrease blood pressure by arteriolar vasodilatation by selectively blocking the slow inward calcium channels in the vascular smooth muscle cells.

Classes of calcium antagonists

Non- dithydropyridine agents

- Verapamil (Calan)
- Diltiazem (Dilzem)

Verapamil has negative inotrpic effect and reduces heart rate by depressing SA node and AV node. Therefore it should not be combined with beta - blocker, combination of both may lead to heart block. Diltiazem has 50% effect on heart and 50% on peripheral vessels causing vasodilatation, it may be combined with beta-blocker but in small dose and very cautiously.

Dihydropyridines

- Amlodipine (Norvasc)
- Nifedipine (Adalat)
- Felodipine (Plendil)

Drugs in this group are mainly vasodilator and minimal effect on heart, therefore they can be combined with beta blockers. They should not be used alone in angina because peripheral vasodilatation causes reflex tachycardia that may aggravate angina.

Advantages of calcium channel blockers

- They are particularly useful when hypertension co-exists with angina.
- They are preferable in black and old patients.
- They are also effective in isolated systolic hypertension.

Side effects

- Headache, flushing, palpitations and peripheral edema (more common with felodipine, nifedipine and amlodipine).
- Bradycardia and constipation (more common with verapamil and to lesser extent with diltiazem.
- Exacerbation of heart failure due to negative inotroic effects.
- Heart block is not an uncommon complication of verapamil (and beta-blockers); always monitor the pulse and educate the patient that these drugs are not for indefinite period. Some patients continue verapamil for years once it is prescribed without further consultation of doctor (to save money) and present in emergency with heart block.

Drug	Initial dose	Dosage range
Verapamil (Celan SR 240mg)	120 mg once daily	120-480 mg in1-2 doses.
Diltiazem (Dilzem SR 180mg)	180mg once daily	180-480mg in1-2 doses
Amlodipine (Norvasc)	5mg once daily	5-20 mg once daily
Felodipine (Plendil)	5mg once daily	5-20 mg once daily
Nifedipine (Adalat retard 20mg)	10-20mg twice daily	10-40 mg twice daily.

ANGIOTENSIN – CONVERTING ENZYMES (ACE) INHIBITORS

Mode of action

They block the conversion of angiotensin I to angiotensin II (a vasoconstrictor) producing arterial and venous dilation.

Advantages

- Useful in hypertension complicated by CHF.
- Helpful in prevention of diabetic nephropathy
- Effective in decreasing left ventricular hypertrophy.
- Relatively less side effects.
- Fosinopril (Monopril) has dual route of excretion (liver & kidney) therefore preferred over other ACE inhibitors in case of renal insufficiency.

Side effects

- Less effective in elderly and predominant systolic hypertension.
- Hyperkalemia may occur especially in patients with diabetes or renal insufficiency.
- First dose hypotension.
- Chronic dry cough due to bronchial or laryngeal irritation more often with captopril and enalapril.
- Skin rash, taste disturbance and leukopenia: more often with captopril.
- Worsening of renal function if given in patient with bilateral renal artery stenosis.
- Angioedema: an uncommon but potentially dangerous side effect. Patient presents with acute dyspnea.

ANGIOTENSIN CONVERTING ENZYME INHIBITORS		
Drug	**Initial dose**	**Dosage range**
Captopril (Capoten)	25mg twice daily	50-300 mg in 2-3 doses
Enalapril (Renitec)	5mg once daily	5-40mg in 1-2 doses
Lisinopril (Zestril)	5-10mg once daily	5-40mg once daily
Fosinopril (Monopril)	10mg once daily	10-80 mg in 1-2 doses
Ramipril (Tritace)	2.5 mg once daily	2.5-20 mg in 1-2 doses
Quinapril (Accupril)	10 mg once daily	10-80 mg in 1-2 doses
ANGIOTENSIN II RECEPTOR BLOCKERS		
Losartan (Cozaar)	50mg once daily	25-100 mg in 1-2 doses
Valsartan (Diovan)	80 mg once daily	80-320 mg once daily

ANGIOTENSIN II RECEPTOR BLOCKERS

Losartan, valsartan are equivalent to ACE inhibitors in efficacy and side effects except incidence of cough is low in receptor blockers.

ALPHA-BLOCKERS

Alpha –adrenergic receptor blockers relax smooth muscles and reduce blood pressure by lowering peripheral vascular resistance. These drugs are most useful in combination with other drugs in less responsive patients. They are drugs of first choice if patient has benign prostate hypertrophy along with hypertension because alpha-blockers reduce symptoms of prostatism (difficulty in urination).

Drug	Initial dose	Dosage range
Prazocin (Minipress)	1mg before sleep	1-20 mg in 1-2 doses
Terazocin (Hytrin)	1mg before sleep	1-20 mg in 1-2 doses
Doxazocin (Cardura)	1mg before sleep	1-16 mg once daily

CENTRAL ACTING DRUGS

- They lower blood pressure by stimulating alpha-adrenergic receptors in the CNS, thus reducing the degree of vasomotor tone.
- They are used as second or third line agent because of their side effects such as sedation fatigue, dry mouth, postural hypotension, impotence, rebound hypertension after withdrawal. Methyldorpa causes hepatitis and hemolytic anemia.
- Methyldopa (Aldomet) 250-500 mg TID
- Clonidine (Catapress) 0.1 mg BID.

Factors that may influence the choice of anti-hypertensive medications

Current strategies favor tailoring drug therapy to the specific needs of the individual patients, especially in view of complicating medical conditions e.g. asthma, vascular disease, and diabetes.

1. **Young hypertensive patients (>35 years)**

   They have increased sympathetic tone and elevated plasma rennin activity. •

   - Diuretics, ACE inhibitors, calcium channel, blockers and combined alpha and beta adrenergic blockers are effective.
   - Beta-blockers alone may cause sexual dysfunction (impotence) and decrease high-density lipoprotein (HDL) cholesterol which is protective and inhibitor of atherosclerosis. Therefore should be avoided.

2. **Old hypertensive patients (>60 years)**
They have increased vascular resistance, decreased plasma rennin activity and greater left ventricular hypertrophy than young patients.
   - Diuretics should be chosen as initial therapy.
   - Calcium channel blocker and ACE inhibitors (although rennin is low) are also effective
   - Drugs that produce postural hypotension e.g. alpha-blockers should be avoided.

4. **Hypertensive with diabetes**
   - ACE inhibitors should be first line therapy in diabetic patients with nephropathy because they reduce proteinuria and slow the progressive loss of renal function independent of their anti-hypertensive effect. Hyperkalemia is common side effect in renal impairment.
   - Beta-blockers should be avoided in diabetics as they can mask the signs and symptoms of hypoglycemia (symptoms of hypoglycemia are produced due to stimulation of sympathetic system). However if patient has concomitant ischemic heart disease then beta –blockers are usually prescribed.

5. **Hypertensive with coronary artery disease**
   - Beta-blockers are first choice in hypertensive patient with angina.
   - ACE inhibitors and calcium channel blocker may be useful.

6. **Hypertensive with chronic renal failure**
   - Diuretics are first line therapy.

7. **Hypertensive with congestive heart failure**
   - ACE – inhibitors first choice
   - Nitrates may be used.

HYPERTENSIVE CRISIS

Hypertensive crisis is the condition when rapid reduction of blood pressure is required. Usually the diastolic blood pressure is >130 mmHg and persistent diastolic blood pressure > 130 mmHg is often associated with vascular damage. In hypertensive *urgency*, blood pressure may be controlled slowly with oral agents. Although blood pressure is very high, usually there is no end organ damage. In hypertensive *emergency*, immediate reduction in blood pressure is required within 1-hour with parenteral drugs to prevent end organ damage

HYPERTENSIVE URGENCY

(Accelerated hypertension)
This is the condition in which blood pressure must be reduced within a few hours. Hypertension is severe when systole blood pressure is > 220 mmHg and diastolic > 125 mmHg. Patient may be asymptomatic or with minimal symptoms and papilledema. Parenteral drug therapy is not required if there is no end organ damage.

HYPERTENSIVE EMERGENCY

This is the condition which requires rapid reduction of blood pressure within one hour to avoid serious morbidity or death. It is characterized by sudden severe increase in blood pressure, associated with acute injury to target organs. Blood pressure is usually > 130 diastolic.

Target organ damage may be the following:

- **Brain:** *Hypertensive encephalopathy* (headache, confusion, irritability, altered mental status and intracranial hemorrhage).
- **Kidney:** *Hypertensive nephropathy* (hematuria, proteinuria, and progressive renal dysfunction).
- **Heart:** Angina, pulmonary edema, or myocardial infarction.
- **Retina:** Hemorrhage, exudates and papilledema.

Urgency is usually severe hypertension without or with minimal symptoms and controlled slowly in 24 hours while emergency is severe hypertension with symptomatic end organ damage.

Malignant hypertension

Malignant hypertension is said to occur when blood pressure rises rapidly and severely (diastolic BP >140 mmHg) causing fibrinoid necrosis of vessel wall, resulting in encephalopathy, stroke, cardiac failure, renal failure with proteinuria and hematuria, papilledema and retinal hemorrhage.

- Encephalopathy presents with severe headache, vomiting, visual disturbances such as transient blindness, transient paralysis, convulsion, stupor and coma. Hypertensive encephalopathy results from cerebral edema or spasm of cerebral vessels. The vascular lesion characteristic of malignant hypertension is fibrinoid necrosis of walls of small arteries and arterioles.
- Severe renal impairment (with proteinuria and microscopic hematuria) is another feature of malignant hypertension.
- Retinal hemorrhages, exudates and papilloedema are diagnostic of malignant hypertension. Without treatment, death occurs within 1-2 years.

MANAGEMENT

Parenteral therapy is indicated in most hypertensive emergencies, especially if encephalopathy is present. Blood pressure should be reduced not more than 25% over a period of 1-2 hours and achieve blood pressure level 160/100 mmHg within 2-6 hours. Rapid fall in blood pressure causes cerebral damage including blindness and may precipitate coronary, cerebral or renal insufficiency.

1. **Sodium nitroprusside (Nipride) IV infusion.**
   - It is a direct acting arterial and venous vasodilator.
   - It is a drug of choice for most hypertensive crises because its action is rapid, easily titrable and short lived when discontinued.
   - Side effects: High dose for 48-72 hours can cause accumulation and toxicity of thiocyanate, a metabolite.

2. **Nitroglycerin (Isoket) IV infusion**

   Nitroglycerin is used when sodium nitroprusside is relatively contraindicated (in severe coronary insufficiency, an advanced renal or hepatic disease). It is given by continuous intravenous infusion at a rate of 5μg/kg/min. It is particularly useful in the treatment of hypertension, after unstable angina, left ventricular failure and myocardial infarction, however it should be avoided in inferior wall myocardial infarction. Most of the time we control blood pressure with nitroglycerine in our setup.

3. **Hydralazine IV bolus**
   - Hydralazine reduces blood pressure by direct relaxation of vascular smooth muscle and may be given I/M or IV. Mainly used in hypertension associated with pregnancy (pre-eclampsia). It produces reflex tachycardia and should be combined with beta-blocker. Dose 10 mg IV every 10-15 min until the desired effect has been achieved or until a total of 50 mg has been given. Hydralazine should be avoided in patient with significant coronary artery disease.

4. **Diazoxide**

   Diazoxide causes arteriolar dilatation and given as a dose of 50-150 mg IV rapidly, antihypertensive effect appears in 1-5 min. The dose can be repeated in 5-10 min. It should not be given if myocardial infarction is suspected.

5. **Labetalol IV bolus**

   The use of labetalol may be of particular benefit in hypertension associated with pheochromocytoma, clonidine withdrawal and cocaine intoxication. It is also effective in patients of myocardial infarction and in eclampsia, if patient is not responsive to hydralazine.

6. **Diuretics**

   Intravenous frusemide is used when patient has signs of heart failure or fluid retention.

7. **Nifedipine (Adalat)**
   - Capsule Adalat 10 mg sublingual or chewing and swallowing reduces blood pressure, onset of effect occurs in 5-10 minutes while peak effect develops within 30-60 min and duration is 3-6 hours. Give 2-3 drops sublingually and monitor the response. Check BP every 15-30 min and give further drops accordingly. Response in unpredictable and sudden fall in blood pressure is the main hazard.
   - Should be avoided in coronary artery disease because it increases heart rate, which may precipitate angina.

REFRACTORY HYPERTENSION

The common causes of treatment failure in hypertension are:

- Non-compliance i.e. patient is not taking drug regularly.
- Inadequate therapy
- Failure to recognize secondary causes of hypertension e.g. renal artery stenosis and phechromocytoma.
- Use of antagonistic drugs e.g. NSAIDS, steroids, cocaine, and thyroxin.
- Increased alcohol intake.

SELECTION OF ANTI- HYPERTENSIVE DRUG IN SPECIAL CASES		
Indication	**Preferably use**	**Avoid**
• Angina	• Beta blocker, calcium channel blocker	Dihydropyridines e.g. nifedipine
• Myocardial infarction	• Beta blocker	Dihydropyridines e.g. nifedipine.
• Atrial fibrillation	• Beta blocker, calcium channel blocker (non-dihydropyridines)	
• Heart failure	• ACE inhibitor, nitrates, diuretics	Calcium channel blocker (except amlodipine).
• Diabetes mellitus	• ACE inhibitors	Beta blocker, high dose diuretic
• Hyperlipidemia	• Alpha blocker	Beta blocker, high dose diuretic
• Hyperthyroidism	• Beta blocker	
• Migraine	• Beta blocker (non-cardioselective) • Calcium channel blocker (nondihydropyridine).	
• Prostatism	• Alpha blocker	
• Osteoporosis	• Thiazides	
• Renal failure (caution in renal artery stenosis and creatinine > 3 mg/dl).	• Calcium channel blocker, ACE inhibitors	Potassium sparing diuretics
• Asthma		Beta blocker
• Depression		Beta blocker, methyldopa and other centrally acting alpha agonists.
• Gout		• Diuretics
• Peripheral vascular disease		• Beta blocker
• Liver disease		• Methyldopa
• Pregnancy	• Methyldopa, calcium channel blocker	• ACE inhibitor.

ISCHEMIC HEART DISEASE (IHD)

Myocardial ischemia develops when there is an imbalance between supply of oxygen and the myocardial demand.

ETIOLOGY

1. **Decreased coronary blood flow due to mechanical obstruction such as:**

- Atheroma – occluding one or more major coronary arteries.
- Spasm of coronary artery
- Thrombosis
- Embolus
- Coronary arteritis (e.g. in SLE)
- Congenital abnormalities of coronary artery.

2. **Increased myocardial oxygen requirement**

- Increased cardiac output: in thyrotoxicosis
- Myocardial hypertrophy: usually from aortic stenosis or hypertension.

3. **Decreased flow of oxygenated blood to myocardium**

- Anemia
- Hypotension – causing decreased coronary perfusion pressure.

4. **Cardiac syndrome X**

   Angina occurring in patient with normal coronary arteries, resulting from disease of coronary microcirculation is called syndrome X. This is also called microvascular angina.

ATHEROSCLEROSIS

The most common cause of myocardial ischemia and angina is the formation of atheroma. Atheroma is a fibrofatty plaque in the intima of large and medium size arteries producing narrowing of the lumen of the vessels. Exact cause of atheroma formation is not known. A 50% reduction in luminal diameter produces a reduction in luminal cross – sectional area of approximately 70% This is considered significant obstruction and patient becomes symptomatic on exertion when increased blood flow is required that can not be supplied according to the demand.

RISK FACTORS FOR ATHEROSCLEROSIS

Risk factors for atherosclerosis may be fixed or modifiable

Fixed risk factors

Age:

Risk increases with age, rare in childhood except in familial hyperlipidemia.

Male sex:

Men have higher incidence of ischemic heart disease than premenopausal women. After menopause the incidence of atherosclerosis in women reaches that in men. This protection in premenopausal women is probably due to estrogen.

Family history:

A positive family history means ischemic heart disease in first-degree relatives before the age of 45 years in male and before 50 years in female.

Modifiable risk factors

(Changeable with treatment)

Strong association

Hyperlipidemia:

High serum cholesterol especially increased low - density lioprotein (LDL) and decreased high-density lioproteins (HDL) is strongly associated with coronary atheroma.

Hypertension

Both systolic and diastolic hypertension are associated with increased risk of coronary artery disease. The risk is same for men and women.

Cigarette smoking

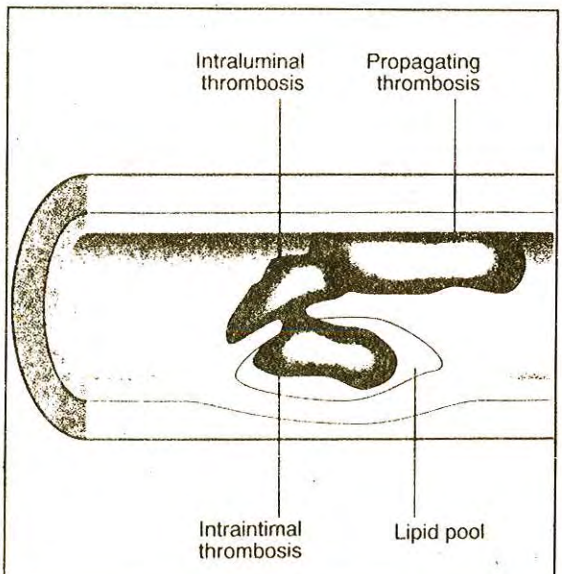
Risk of coronary artery is directly related to number of cigarette smoked. The risk from smoking declines to almost normal after ten years of quitting.

Diabetes mellitus

Diabetes or even just an abnormal glucose tolerance test is strongly associated with vascular disease.

Other associations

1. **Obesity:** particularly central or truncal obesity.
2. **Lack of exercise:** regular exercise for 20 minutes 2-3 times/week protects from coronary heart disease.
3. **Heavy alcoholism:** moderate intake of alcohol (2-4 units a day) appears to offer some protection from coronary disease: however, heavy drinking is associated with hypertension and an excess of cardiac events.
4. **Dietary factors:** diet deficient in fresh fruit, vegetable and polyunsaturated fatty acids are associated with an increased risk of coronary artery disease. Low levels of vitamin C, vitamin E and other antioxidants may enhance the production of oxidized LDL that is an important risk for coronary artery disease.
5. Oral contraceptives
6. Gout.
7. Infection with chlamydia pneumonia, helicobacter pylori and CMV.
8. High level of coagulation factor VII and fibrinogen.
9. Elevated plasma homocysteine level. Folic acid in low doses may prevent from its atherogenic effect.
10. **Raised C-reactive protein (CRP).**
11. High plasma lipoprotein (a).
12. Anxiety and depression.



NON-ATHEROSCLEROTIC CAUSES OF CARDIAC ISCHEMIA

1. **Embolism:** source of emboli may be:
   - Infective endocarditis
   - Mural thrombi in left atrium or ventricle
   - Thrombi from prosthetic valves
   - Intracardiac tumors
   - Paradoxical emboli from venous system across ASD or VSD
2. **Chest wall injury**: causing injury to coronary arteries resulting in intracoronary thrombosis.
3. **Mediastinal radiations:** causing fibrosis of coronary arteries.
4. **Aortic dissection:** may propagate to aortic root and occlude coronary artery at its origin.
5. **Coronary artery dissection** in angiography or angioplasty.
6. **Vasculitis:** syphilis, Takayasu's arteritis, polyarteritis nodosa, SLE, giant cell arteritis, Kawasaki's disease resulting in coronary aneurysm.
7. **Blood disorders causing intracoronary thrombosis**:
   - Polycythemia vera, DIC, sickle cell anemia.
8. **Congenital coronary anomalies**
9. **Spontaneous coronary spasm:** with or without underlying coronary artery disease.
10. **Mismatch of myocardial oxygen supply and demand:**
- Thyrotoxicosis
- Aortic stenosis
- Aortic regurgitation
- Tachyarrhythmias
- Sepsis

12. **Decreased oxygen delivery**
- Acute blood loss
- Hypotension
- Anemia
- Carbon monoxide poisoning

CORONARY ARTERY DISEASE

Coronary artery disease is the most common cause of death. It is almost always caused by atheroma and its complication such as thrombosis. There are certain presentations of coronary artery disease such as:

1. Stable angina
2. Unstable angina
3. Myocardial infarction
4. Heart failure
5. Arrhythmia
6. Sudden death

ANGINA PECTORIS

Angina pectoris is a clinical syndrome characterized by paroxysmal chest pain due to transient myocardial ischemia. It may occur whenever there is imbalance between myocardial oxygen supply and demand. The most common cause is atherosclerosis; however angina may also develop in aortic stenosis (AS) and hypertrophic cardiomyopathy (HOCM) even there is no coronary atheroma.

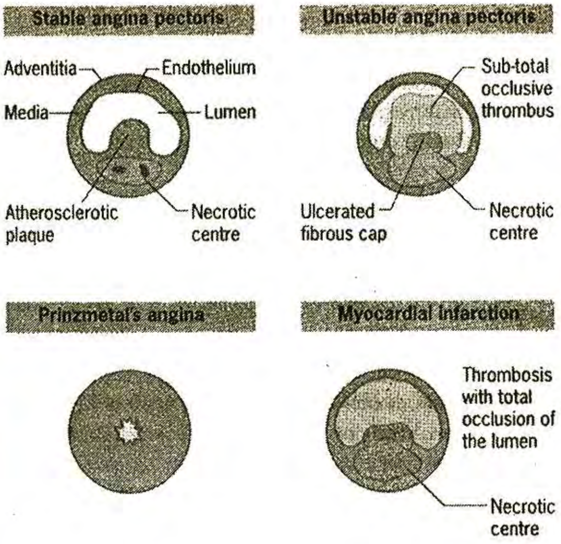
PATHOPHYSIOLOGY OF STABLE ANGINA, UNSTABLE ANGINA AND MYOCARDIAL INFARCTION

Stable angina:
Stable angina is the angina that occurs when coronary perfusion is impaired by fixed or stable atheroma of coronary arteries i-e patient has fixed capacity of exertion after that he starts feeling chest pain.

Unstable angina:
Unstable angina is the angina that is characterized by rapidly worsening chest pain, pain on minimal exertion or pain at rest. The culprit lesion is usually a complex ulcerated or fissured atheroma with adherent platelet – rich thrombus and local coronary spasm.

- Unstable angina = ulcerated atheroma + thrombus formation → abrupt reduction of coronary blood flow caused by thrombus formation → angina at rest.

Myocardial infarction
Pathophysiology of unstable angina and myocardial infarction is same (i-e thrombus formation on atherosclerotic plaque) however in unstable angina obstruction of artery is incomplete while in MI there is total obstruction.



Relationship between the state of coronary artery vessel wall and clinical syndrome.

TYPES OF ANGINA

1. Classical or exertional angina

It occurs due to increased myocardial oxygen demand during exertion or emotion in a patient of narrow coronary arteries. It is relieved promptly by rest and by nitroglycerine.

2. Variant or Prinzmetal's angina

It occurs at rest and is not a result of increased myocardial demand. It is produced by the episodic reduction of myocardial blood supply due to coronary artery spasm. Underlying atherosclerotic disease may or may not be present. This type of angina occurs more frequently in women (under age 50 years) especially early in the morning, awakening patients from sleep and the pain is usually more severe and more prolonged than in classical angina. It tends to involve right coronary artery. It is characteristically associated with ST elevation rather than depression (as seen in classical angina).

3. Unstable angina

Unstable angina refers to angina of recent onset (less than one month), worsening angina characterized by increased frequency and duration of episode, or angina at rest not responding readily to therapy.

4. Decubitus angina

This is angina that occurs when the patient lies down. It usually occurs in association with impaired left ventricular function. Patient with this symptoms usually has severe coronary artery disease.

5. Nocturnal angina.

This is the angina that awakes the patient from sleep. It may be provoked by vivid dreams. It may occur due to critical coronary artery obstruction or coronary spasm.

6. Cardiac syndrome X

Patient presents with angina, positive exercise test (ETT) and angiographically normal coronary arteries. It may be because of functional abnormalities of coronary microcirculation (no dilatation of arterioles at the time of stress).

CLINICAL FEATURES OF STABLE ANGINA

SYMPTOMS

1. Chest pain
2. dyspnea
3. Associated symptoms

Typical angina pain

Site:

Pain may arise in one of the following sites.

- Middle or lower sternum (mostly)
- Left precordium
- Epigastrium
- Left shoulder or left upper arm
- Lower jaw
- Interscapular region

Pricking pain for few seconds especially near left nipple is very common and usually non-cardiac.

Radiation

Pain can radiate to any dermatome from C8 to T4, it radiates most often to the left shoulder and left arm, moving down to elbow and ulnar aspect of forearm , wrist or 4th and 5th finger. Other sites of radiation are:

- Left shoulder, both arms
- Back of neck
- Lower jaw
- Interscapular region
- Right chest
- Eigastrium

Character

Patient feels tightness in the chest "like a band around the chest" while describing he commonly laces the hand or clenched fist n the sternum (fist sign). He may also describe it as a sense of pressure, choking or heaviness in the chest. The pain may be sharp and piercing.

Duration

Anginal pain lasts only a few minutes, less than 30 minutes but mostly it remains for 1-4 minutes. It subsides completely without residual discomfort.

Aggravating (precipitating factors)

- Physical exertion e.g. exercises, sexual activity.
- Heavy meals.
- Intense emotion e.g. stress, anger, fright or frustration.
- Lying flat (decubitus angina).
- Violent dreams (nocturnal angina).
- Pain may occur at rest such as variant and unstable angina.

Dyspnea

Associated symptoms

- Feeling of uselessness in the limbs
- Dizziness or fainting
- Chocking sensation in throat
- Polyuria after an attack.

SIGNS

During attack patient looks anxious. Dyspnea, pale face, and cold sweats may also be present. In between attacks, physical examination is frequently negative except findings of risk factors.

Search for the evidence of the following:

- Risk factors: e.g. hypertension, hyperlipidemia (such as tendon xanthomas), diabetes, myxoedema.
- Contributory factors: e.g. obesity, anemia, thyrotoxicosis and aortic valve disease.
- Left ventricular dysfunction such as gallop rhythm, cardiomegaly and basal crepitations.
- Generalized arterial disease e.g. carotid bruits, peripheral vascular disease.

DIFFERENTIAL DIAGNOSIS

Following diseases may cause pain in the chest and mimic angina.

Musculoskeletal

- Intercostal neuritis due to herpes zoster and diabetes etc.
- Myalgia of chest wall.
- Tietze syndrome: inflammation of chondrosternal joints causing chest pain and tenderness.
- Cervical or thoracic spine disease involving the dorsal roots, produces sudden sharp severe chest pain suggesting angina in location and radiation, but related to specific movements of the neck or spine, recumbency and straining or lifting. This pain involves outer or dorsal aspect of the arm and the thumb and index finger rather than the ring and little fingers.

Cardiovascular conditions

- Pericarditis
- Dissecting aortic aneurysm

Pulmonary conditions

- Pleurisy due to pneumonia or tuberculosis
- Pulmonary embolism
- Spontaneous pneumothorax

GIT conditions

- Esophagitis, esophageal spasm
- Peptic ulcer and functional gastrointestinal disease.

The Canadian Cardiovascular Society grading of angina of effort.

Grade 1 Ordinary physical activity does not cause angina (strenuous physical activity provokes angina).

Grade II Slight limitations of ordinary physical activity (climbing more than one flight of stairs or walking uphill provokes angina).

Grade III Marked limitation of ordinary physical activity (walking on the level or climbing one flight of stairs provokes angina).

Grade IV Inability to carry on any physical activity (angina may be present at rest).

INVESTIGATIONS

1. ECG

- During pain ECG shows ST – segment depression with or without T wave inversion that reverses after ischemia disappears.
- Elevation of ST segment in prinzmetal's angina.
- The resting ECG may be normal between attacks however it may show old myocardial infarction, heart block or left ventricular hypertrophy.

Differential diagnosis of ST segment depression

1. Myocardial ischemia (angina)
2. Left ventricular hypertrophy
3. Severe hypertension
4. Cardiomyopathy
5. Anemia
6. Preexcitation syndrome
7. Hypokalemia
8. Hyperventilation
9. Digitalis effect

Differential diagnosis of ST segment elevation

1. Myocardial infarction
2. Prinzmetal's angina
3. Ventricular aneurysm (after MI)
4. Acute pericarditis
5. Normal variant (early repolarization)
6. LBBB, LVH (V1-V2 or V3 only)
7. Myocarditis
8. Tumor invading the left ventricle
9. Trauma to the ventricles
10. Hypothermia
11. After DC cardioversion
12. Intracranial hemorrhage
13. Hyperkalemia, hypercalcemia (usually localized to V1-V2

2. EXERCISE TOLERANCE TEST (ETT)

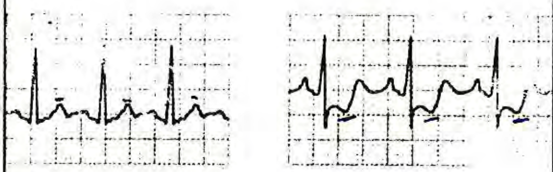
This is the most useful noninvasive procedure for evaluating the patient with angina. Ischemia that is not present at rest is detected by precipitation of typical chest pain or ST segment depression during exercise using treadmill (Jogging machine).

When history is suggestive of angina pectoris but ECG is normal, then the exercise tolerance test should be done.

- This test involves recording the 12- lead ECG before, during and after exercise. The test consists of a standardized incremental increase in external workload while the patient's ECG, symptoms and blood pressure are continuously monitored. A variety of exercise protocols are utilized, the most common being the **Bruce protocol** which increases the treadmill speed and elevation every 3 minutes until limited by symptoms.
- This test discovers any limitation in exercise performance and establishes the relationship between chest pain and typical ECG signs of myocardial ischemia.
- Positive test is one in which ST segment is depressed by 1 mm (one small square).
- More severe disease presents with ST depression >2 mm at low work load (in 6 minutes) or at heart rate <70% of age predicted value, or hypotension develops during exercise.
- When you are reading the report of ETT look at the particular aspects such as:
  - Degree of ST depression.
  - Development of arrhythmia or conduction defect during and post exercise period.
  - Duration of exercise
  - Maximal work capacity (the amount of work performed) is expressed in METs (metabolic equivalent). Number of METs indicates the functional capacity.
  - Achievement of age predicted target heart rate (220 minus age)
  - Development of chest pain during exercise.
  - Hemodynamic response (normally systolic BP rises with exercise).
  - Heart rate response (heart rate increases with exercise)

Exercise test is immediately terminated when there is:-

- Significant chest pain
- Drop in systolic BP of >10 mmHg of baseline.
- Arrhythmias (VT, SVT, multifocal PVCs or heart block).
- Severe dyspnea
- Dizziness, ataxia, fatigue, pallor or cyanosis.
- ST segment depression of > 3-4mm.
- ST segment elevation > 1mm.



Electrocardiographic changes on exercise.
Left trace – at rest. Right trace – during exercise, showing positive ST segment depression.

Indications

- To confirm the diagnosis of angina.
- To determine the severity of limitation of activity due to angina.
- To assess prognosis in patient with known coronary disease, including those recovering from myocardial infarction, by detecting groups at high or low risk.
- To evaluate response to therapy.

Contraindications

- Acute myocardial infarction (< 2 days)
- High risk unstable angina.
- Decompensated heart failure.
- Cardiac arrhythmias with symptoms.
- Heart block
- Acute myocarditis and pericarditis
- Severe symptomatic aortic stenosis
- Severe hypertrophic obstructive cardiomyopathy.
- Uncontrolled hypertension.
- ECG showing I.H.D changes at rest
- Patient who develops pain on mild to moderate activity (exercise intolerant).

Interpretation

Overall sensitivity of ETT is about 60 -75% and specificity 80%. The test may be falsely positive or negative in 15% of cases therefore negative test does not rule out ischemic heart disease and positive test without symptom does not always confirm ischemic heart disease. Test accuracy is increased when multivessel disease is present. If

the ETT is inconclusive then ischemic heart disease should be confirmed by thallium scan, echocardiography and angiography.

False positive

Chances of positive ETT without coronary artery disease increase in the following conditions:

- Asymptomatic men under 40 year of age or premenopausal women.
- Patient taking digitalis or quinidine.
- Patients with intraventricular conduction disturbances.
- Ischemic changes on ECG at rest.
- Myocardial hypertrophy.
- Abnormal serum potassium level.

False positive ETT is uncommon when a 2mm depression is present.

False negative

ETT may be falsely negative if obstruction is limited to circumflex artery since the posterior portion of the heart which this vessel supplies, is not well represented on the surface 12-lead ECG.

ISOTOPE SCANNING

Thallium scan and Technetium scan show areas of diminished uptake of radioactive isotope (thallium or technetium) by the myocardium. This test is performed at rest and during stress (produced by exercise or dipyridamol or dobutamine).

A perfusion defect present during stress but not at rest indicates reversible myocardial ischemia, whereas a persistent perfusion defect on scan during both phases (rest and stress) usually indicates previous myocardial infarction.

Thallium scanning is positive in 75-90% of patients with significant coronary disease. False positive test may occur in women due to breast tissue.

Indication

- When ETT is not diagnostic (equivocal or contrary to the clinical impression such as positive test in asymptomatic patient).
- When resting ECG makes the exercise ECG difficult to interpret (due to LBBB, baseline ST segment changes, low voltage).
- When patient is unable to perform exercise e.g. patient of unstable angina, aortic stenosis or handicapped patient. In these patients stress is produced by alternative methods such as drugs e.g. dipyridamol (Persantin), dobutamine or adenosine.
- To distinguish ischemia from infarction of myocardium.
- To localize the region of ischemia.
- To identify whether the myocardium is viable or not, because revascularization via surgery or angioplasty may be beneficial only for viable myocardium.

ECHOCARDIOGRAPHY

It reveals segmental wall motion abnormalities which indicate ischemia or prior infarction. It can be performed at rest while sensitivity increases if performed after exercise or stress given by dobutamine (called dobutamine stress echocardiography).

CORONARY ANGIOGRAPHY

Coronary angiography visualizes the location and severity of coronary artery stenosis. Narrowing greater than 50% of the luminal diameter is considered clinically significant, although most lesions producing ischemia are associated with narrowing in excess of 70%.

Indications

1. Coronary angiography is indicated in patients in whom coronary revasculariation (angioplasty or by-pass) is being considered because of uncontrolled stable angina who have failed to improve on adequate medical regimen.
2. It is also performed to diagnose chest pain of uncertain cause when non-invasive tests have failed to detect the cause. Diagnostic angiography is now rarely performed because diagnosis of coronary artery disease is usually made on history and non- invasive tests.
3. Unstable angina.
4. Postmyocardial infarction angina.
5. Severe left ventricular dysfunction after myocardial infarction.
6. Non- Q wave MI
7. Strongly positive ETT.

MANAGEMENT

General measures

- Do not smoke
- Aim at ideal body weight
- Take regular exercise – exercise up to, but not beyond point of chest pain is beneficial.
- Avoid severe unaccustomed exertion, vigorous exercise after a heavy meal, or in vary cold weather.
- Take sublingual nitrate before any physical exertion that may induce angina.

Specific

Management can be divided into medical and surgical management.

MEDICAL MANAGEMENT

Medical management consists of the following steps:

- Explanation and reassurance to the patient.
- Advise for adaptation of physical activity.
- Identification and treatment of risk factors and precipitating factors.
- Treatment of acute attack.
- Prevention of attack.

TREATMENT OF ACUTE ATTACK

Sublingual nitroglycerine (Angised) is the drug of choice; it acts in about 1-2 minutes. It reduces arteriolar and venous tone therefore reducing afterload and preload. It also dilates collateral channels. Sublingual nitroglycerine may be repeated at 3-5 min intervals. Pain not responding to 3 tablets or lasting more than 20min may represent evolving myocardial infarction, and patient is instructed to seek medical attention.

Nitroglycerine buccal spray is also available by the name of Nitromint and Nitrplingual spray; 1-2 spray below the tongue.

PREVENTION OF FURTHER ATTACK

There are three principal groups of drugs which help to prevent the symptoms of angina:

1. Nitrates
2. Beta-blockers
3. Calcium antagonists

Other associated drugs

- Aspirin
- Lipid lowering therapy (statins)

NITRATES

Mode of action

They decrease workload on the heart and therefore reduce myocardial oxygen requirement by the following mechanism:

- They relax vascular smooth muscles and thus dilate arterioles that reduces peripheral vascular resistance (reduction in after-load).
- Owing to peripheral venous dilatation blood is pooled in the veins and the venous return is reduced (reduction in pre-load).
- They also dilate the coronary vessels.

> ***Mode of action of nitrates***
> Nitrates reduce pre-load & after-load and dilate the coronary vessels.

Preparations

Short acting nitrates

Glyceryl trinitrate (Angised)

Glyceryl trinitrate (sublingually relieves pain within 2-3 minutes.

- The best use of glyceryl trinitrate (GTN) is prophylactically before exercise known as liable to produce pain.
- Not more than 2 tablets per hour should be used.
- After relieving pain, the tablet should be swallowed to avoid the headache which will be more intense if the tablet remains in the mouth. On swallowing it becomes ineffective.

Intravenous nitroglycerine (Inj. Isoket).

Intravenous nitroglycerine is used in the dosage of 5-15μg/min in unstable angina.

Long acting nitrates

Isosorbide dinitrate (Isordil, Sorbide nitrate 10 mg)

Isosorbide dinitrate 10-40mg three times a day.

Isosorbide mononitrate (Monis, Ismo 20mg)

Isosorbide mononitrate is given as 10-40 mg twice daily.

Sustained – release nitroglycerine (Sustac)

Sustained –release nitroglycerine is available in 2.6mg and 6.4mg. Dosage ranges 2.6 – 12.8 mg 2-3 times daily.

Nitroglycerine transdermal patch (Nitroderm TTS). It provides 0.4-1.2mg/hr nitroglycerine for 12-14 hours. Patch should be removed overnight to avoid nitrate tolerance.

Side effects

1. Headache (more common).
2. Flushing, dizziness
3. Hypotension
4. Tolerance: the main limitation of nitrate therapy is tolerance that can be minimized by 8-10 hour nitrate free period.

BETA BLOCKERS

Mode of action

They reduce myocardial oxygen demand by reducing the heart rate, force of cardiac contraction and therefore decreasing the cardiac output. Beta-blockers are the only anti-anginal agents that have demonstrated to prolong life in patients with coronary disease, therefore they should be considered for first-line therapy in most patients with chronic angina. Atenolol and metoprolol are most commonly used.

Preparations

- Atenolol (Tenormin 50, 100mg) 50-150 mg once daily.
- Metorolol (Mepressor 100mg) 25-200 mg twice daily.
- Propranolol (Inderal) 20-80mg 4-tmes daily.
- Bisoprolol (Concor 5mg, 10mg) 2.5-20mg once daily.
- They should not be withdrawn abruptly because of rise of dangerous arrhythmias and myocardial infarction.

Side effects

- Fatigue, and impotence
- Insomnia, depression and nasal congestion (more common with propranolol).
- Adverse effects on lipid profile; increased triglyceride and decreased HDL.
- Deterioration of CHF, bronchospasm, hyperglycemia and peripheral vascular disease.
- Abrupt withdrawal can precipitate angina.

CALCIUM AGONISTS

Mode of action

They block inward movement of calcium ions into the cardiac muscle cells, smooth cells of coronary and systemic arteries. Therefore they reduce systemic and coronary resistance. In this way they decrease workload on the heart and increase oxygen availability.

In combination therapy beta-blockers are first combined to nitrates, if the patient remains symptomatic then calcium channel blockers are added. Calcium channel blockers can be combined with nitrate instead of beta-blockers if the beta-blockers are contraindicated.

Combination of beta-blocker and verapamil should be avoided because it can lead to heart block. Diltiazem in smaller dose (usually 30mg 3-times daily) can be combined with beta-blocker. Amlodipine or long acting nifedipine are combined with nitrates when beta blocker is also combined otherwise reflex tachycardia may develop due to peripheral vasodilatation caused by amlodipine or nifedipine causing worsening of the angina.

Preparations

- Nifedipine (Tab. Adalat retard 20 mg) twice daily.
- Nifedipine (Tab. Adalat CC 30 and 60 mg). Usual dosage is 30-90mg once daily.
- Diltiazem (Tab. Dilzem SR 180 mg) twice daily.
- Amlodipine (Norvasc 5mg) 5-10 mg once daily.
- Verapamil (Tab. Calan SR 240 mg). Usual dosage is 180-240 mg once daily.

Side effects

Verapamil and diltiazem: Constipation, heart block and worsening of heart failure.

Nifedipine, amlodipine: Hypotension, flushing, edema and worsening of angina (due to reflex tachycardia).

ASPIRIN:

It is a platelet-inhibiting agent preventing coronary thrombosis that is responsible for most episodes of myocardial infarction and unstable angina.

Therefore small dose aspirin ½ - 1 tablet daily is advised to all patients unless contraindicated. If patient is intolerant to aspirin ticlopidine (Ticlid 250 mg) twice daily or clopidogrel (Noclot 75 mg) once daily may be used for antiplatelet effect.

REVASCULARIZATION

Indications of revascularization in the form of either angioplasty or bypass (CABG) are as following:

- Patients with unacceptable symptoms despite maximum tolerable medical therapy.
- Patients with left main coronary artery stenosis > 50% with or without symptoms.
- Patient with three-vessel disease with left ventricular dysfunction (ejection fraction < 50%) or previous myocardial infarction.
- Patients with unstable angina who after symptom control by medical therapy continue to exhibit ischemia on exercise testing or monitoring.
- Post myocardial infarction patients with continuing angina or severe ischemia on non-invasive testing.
- Two vessel disease associated with:
  - Underlying left ventricular dysfunction.
  - Anatomically critical lesion (> 90% proximal stenosis, especially of the proximal left anterior descending artery)
  - Physiological evidence of ischemia (early positive ETT, large reversible defect on thallium scan, or frequent ischemia on Holter monitoring)

CHOICE OF REVASCULARIZATION PROCEDURE ANGIOPLASTY OR SURGERY (PTCA OR CABG).

PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY (PTCA)

Percutaneous transluminal coronary angioplasty (PTCA) is performed by passing a fine guide-wire with deflated balloon through femoral artery, retrograde up to the aorta and into diseased coronary artery. The balloon is then positioned across the stenotic area and inflated under pressure. This results in fracture of atherosclerotic plaque. The lumen can be successfully dilated in greater than 90% of cases. Now the metallic stent is inserted that significantly reduces the chances of restenosis.

PTCA is superior to medical treatment in relieving angina. Short, concentric, soft lesions on a straight segment of artery are ideal for this treatment. On the other hand, the outcome tends to be worst if the target lesion is complex, eccentric, calcified or lies on a bend of artery.

Indications:

1. Symptomatic single or two-vessel disease (not left main artery disease) with normal left ventricular function and anatomically suitable lesion is advised initially to undergo PTCA.
2. Stenosis in bypass graft (but surgery is preferred)

Complications

1. Intimal dissection forming thrombus that occludes the vessel requiring repeat PTCA or urgent CABG otherwise leads to myocardial infarction. This complication of thrombus formation may be prevented by the use of glycoprotein IIb/IIIa inhibitors (Aggrastat) during procedure in high risk patients (such as patients of unstable angina or MI), and use of clopidogrel (Plavix 75 mg) daily for one month and aspirin daily indefinitely.
2. Chance of re-stenosis in first 6 months is 30-50% of vessels dilated when only balloon angioplasty is performed while < 20% of vessels when stent is also used. Restenosis after use of newer drug eluting stents is 4 -5 %; however the cost is also three times higher.

CORONARY ARTERY BYPASS GRAFTING (CABG)

It is a major surgical method in which narrowed segments of coronary artery are bypassed using either free grafts of saphenous vein or the patient's internal mammary artery. Radial artery graft is also commonly used now. Graft is sutured between aorta and coronary arteries distal to the obstruction.

- The procedure is safe, with mortality rate < 1-3 % in patients with preserved cardiac function and it rises to 4-8% in older individuals and in patients who have had a prior CABG (this is Western data). Operative mortality rate is increased in patients with

ejection fraction < 35%, age over 70 years, repeat procedure, diabetes or renal failure.

- Mortality is higher in Pakistan mainly due to lack of postoperative care; therefore before sending the patient to a particular surgeon and hospital first inquire from hospital staff and other patients about the mortality and complication rate of that particular surgeon.
- Occlusion of grafts is observed in 8-12% of venous grafts early before hospital discharge, 15-30% during first postoperative year and then 2% per year till 6 years then 4% per year. After 10 years 50% of venous grafts are closed and there is significant atherosclerosis in remaining grafts. High LDL, low HDL, small vessels, prior MI, male gender and active smoking are the predictors of graft occlusion. Survival is better when left internal mammary artery (LIMA) graft is used Dissection and grafting of LIMA is comparatively difficult and requires better skill.
- Angina is abolished or greatly reduced in approximately 90% of patient.
- CABG is a palliative measure not cure of coronary artery disease, it abolishes symptoms. Survival benefit over medical therapy is seen only in the following patients.
  - Significant left main coronary artery disease.
  - Multivessel disease with left ventricular dysfunction (due to ischemia).
  - Triple vessel disease with proximal LAD (even without LV dysfunction).
  - Two vessel disease with LV dysfunction with proximal narrowing of one or more coronary artreries.
  - Single vessel disease with narrowing of proximal LAD and LV dysfunction.

TYPES OF CABG

- Conventional CABG
- Minimally invasive CABG

Conventional CABG is performed by incision in the sternum, stopping the heart and use of cardiopulmonary bypass pump. Complications of conventional bypass surgery are mainly related to heart-ung machine (cardiopulmonary bypass pump) and to large sternal incision. Now a days, minimally invasive procedures are also routinely performed in which operation is performed without stopping the heart and use of bypass pump or the very small incision is given in intercostals space on left side of chest. There are two types of minimally invasive procedures:

- ***MIDCAB:*** Minimally Invasive Direct Coronary Artery Bypass Grafting: In this procedure incision is small and on left side of chest. Operation may be performed with or without bypass pump (i.e. on beating heart). This procedure is only suitable for front side coronary vessels such as left anterior descending artery (LAD) and its diagonal branches; multiple vessel grafting is not possible.
- ***OPCAB:*** Off-Pump Coronary Artery Bypass Grafting: In this procedure incision is given in sternum just like in conventional CABG; however it is performed on beating heart without bypass pump.

Advantages of minimally invasive procedures:

- Avoidance of cardiopulmonary bypass lessens the risk of bleeding, thromboembolism, renal failure, left ventricular dysfunction, cerebral complications such as stroke and impairment of memory.
- Small incision allows earlier postoperative mobilization and discharge from the hospital and minimizes risk of wound infection.

INDICATIONS OF CABG

Unacceptable level of angina despite optimal medical treatment should undergo revascularization. Coronary artery bypass grafting CABG is preferred to PTCA in patients with the following factors:

- Left main coronary artery disease
- Severe three-vessel disease (significant proximal stenosis), particularly those with impaired left ventricular function (ejection fraction < 45%) (because function improves after surgery).
- For symptom control in patients who remain symptomatic despite optimal medical therapy and whose disease is not suitable for angioplasty.
- Patient is diabetic.
- Lesion is not suitable for PTCA.

COMPLICATIONS

- Diffuse left ventricular damage due to ischemia.
- Peri-opoerative MI
- Respiratory complications requiring prolonged intubation period after CABG.
- Bleeding
- Wound infection
- Atrial fibrillation.
- Complications of anesthesia.
- Renal failure
- Cerebral complications: (usually due to emboli or hypotension) stroke, stupor, coma, deterioration of intellectual function and memory.

RISK FACTORS

LEADING TO INCREASED COMPLICATIONS AND MORTALITY IN CABG.

Preoperative factors:

Old age, diabetes mellitus, comorbidity such as pulmonary or renal disease, recent acute MI, hemodynamically instability, left ventricular dysfunction, previous bypass surgery, extensive atherosclerosis, presence of left main coronary artery disease and unstable angina.

Operative factors:

Intraoperative ischemic damage of myocardium (a common factor of morbidity and mortality by incompetent surgeon).

Postoperative factors

Improper postoperative care of patient especially initial 24-48 hours (not uncommon factor in our hospitals due to negligence of nursing staff and junior doctors).

EXPERIMENTAL APPROACH TO TREAT ANGINA

Some patients remain symptomatic despite medication and are not suitable for revascularization (e.g. diffuse disease). In these patients relief from angina may be achieved with some non- pharmacological treatment as following:

Mechanical extracorporal counterpulsation

It includes repetitive inflation of a high pressure chamber surrounding the lower half of the body during the diastolic phase of cardiac cycle for daily 1- hour sessions over a period of 7 weeks.

Spinal cord stimulation

In this procedure a flexible electrode is used in the epidural space at the mid- thoracic level. Stimulation via a pacemaker – like generator reduces angina.

ANGINA WITH NORMAL CORONARY ARTERIES

About 10% of patients with angina on exertion are found to have normal coronary arteries. Exact mechanism is unknown but coronary artery spasm or syndrome X may be the underlying mechanism.

TREATMENT OF VARIANT ANGINA

Nitrates and calcium antagonists are useful, but beta-blockers should be avoided because they may increase coronary tone.

UNSTABLE ANGINA AND ACUTE CORONARY SYNDROME (ACS)

Unstable angina is a clinical syndrome characterized by angina of new onset, angina at rest or with minimal exertion or episodes of increasing frequency, severity or duration Rupture or fissuring of atherosclerotic plaque resulting in thrombus formation and vessel occlusion is the cause of unstable angina (incomplete occlusion in unstable angina and complete occlusion in MI). This unstable condition may lead to complete occlusion of vessel causing myocardial infarction or healing may take place returning to stable ischemia. It carries 10-20% risk of progression to acute myocardial infarction, therefore it is a common reason for hospitalization.

Acute coronary syndrome (ACS) includes unstable angina and non- ST elevation MI. ECG shows ischemic pattern such as ST segment depression or T wave flattening or inversion. If cardiac enzymes are not elevated, this is unstable angina and if enzymes are elevated this is non- ST elevation MI (NSTEMI). Most of the patients admitted in cardiology hospital have the diagnosis of ACS. There may be signs of left ventricular dysfunction during pain.

Investigations

Serial ECGs and serial cardiac enzymes including Troponin T or Troponin I.

MANAGEMENT

- Hospitalization
- Strict bed rest, supplemental oxygen
- Sedation with a benzodiazeine if there is anxiety.
- Systolic blood pressure is maintained at 100-120 mmHg and pulse should be lowered to 60/min.
- Heparin, antiplatelets, nitrates and beta-blockers are the main pharmacological treatment.
- Revascularization

Anticoagulation and antiplatelet therapy

Because intravascular thrombosis plays prominent role in the pathophysiology of ACS, antithrombotic therapy is an important part of treatment as following:

Heparin: Intravenous unfractionated heparin or preferably low molecular weight (LMW) heparin given subcutaneously should be continued for at least 2-3 days.

- *Enoxaprin (Clexane)* 1mg/kg S/C is given 12- hourly. (a low molecular weight heparin).

Anti-platelets

- *Aspirin:* Half- to one tablet daily as an antiplatelet agent.
- *Clopidogrel (Plavix 75mg)* 4 tablets stat as a loading dose and then one daily for 12 months. It is an anti-platelet agent, when combined with aspirin causes 20% reduction in cardiovascular death and MI compared with aspirin therapy alone. Ticlodipine (Ticlid 250 mg) twice daily also belongs to the clopidogrel group, cheaper but causes thrombocytopenia and neutropenia in about 1% of cases; therefore clopidogrel is preferred.
- *Glycoprotein IIb/IIIa inhibitors*
  Eptifibatide, abciximab and tirofiban are the very strong antiplatelet agents used in high risk patients receiving predominantly medical treatment or early interventional management (angioplasty). Patients going to early angioplasty get greater benefit with these agents. Eptifibatide (Aggrastat) 180μg/kg bolus followed by a continuous infusion of 0.1 μg/kg/min. Abciximab and tirofiban may also be used.

No role of thrombolytic therapy

Since in unstable angina the vessels are not fully occluded and thrombi are undergoing continuous spontaneous formation and thrombolysis through body's own anticoagulants, thrombolytic therapy (e.g. streptokinase) is not effective in improving the outcome. Even it may be harmful because there is prothrombotic effect of thrombolysis in unstable angina.

Nitrates

Nitrates are one of the cornerstones of therapy. They are first line anti-ischemic treatment. Nitrates should initially be given sublingually, if pain persists after 3 sublingual tablets given 5 minutes apart IV nitroglycerine 5-10μg/min is recommended. In the acute phase it is preferable to use intravenous nitroglycerin to ensure adequate bioavailability, a rapid onset and easy dose titerability. Nitroglycerin (Isoket) IV infusion started at a rate of 5-10μg/min, may be increased

by 10μg/min every 3-5 min until symptoms are relieved or systolic blood pressure falls to below 100mmHg in the first 24-48 hours. A dose of 200μg/min may be given. Headache, hypotension and bradycardia are side effects. Oral or sublingual nitrates are better suited for subacute or chronic use.

Nitrates may reduce symptomatic and asymptomatic episodes of ischemia but there is no effect on incidence of myocardial infarction or on mortality (i.e. it relieves pain but does not prevent MI).

Beta- blockers

Beta-blockers are also a part of initial treatment of unstable angina unless otherwise contraindicated. In emergency intravenous metoprolol (Lopressor 5mg) given three injections 5 minutes apart to achieve heart rate 60-70/min. Oral therapy may also be used. Beta -blockers reduce subsequent MI and recurrent ischemia.

Calcium channel blockers

Because exaggerated vasoconstriction may play a role in unstable angina, calcium channel blockers have been used in the management of unstable angina, however calcium channel blockers are second choice (beta-blockers first) and should be used if there is persistent ischemia after treatment with full- dose nitrates and beta- blockers or beta-blocker is contraindicated. Diltiazem and verapamil may be used. If nifedipine or amlodipine is used it must be combined with beta -blocker.

ACE inhibitors

ACE inhibitors should be started early within 24 hours, as it shows 0.5% mortality benefit.

Revascularization

High risk patients who do not become ischemia free on medical therapy should have early coronary angiography and revascularization usually within first 48 hours of presentation. High risk patients are those with recurrent ischemia, congestive heart failure, ST segment changes on ECG, positive cardiac enzymes (Trop T) and the patients presenting with unstable angina within 6 months of angioplasty.

Angiography [illegible] shows thrombus in coronary artery, therefore IIb/IIIa inhibitor such as Aggrastat is started before angioplasty and continued for 24 hours after procedure to prevent abrupt closure of the stent and occurrence of MI. Bypass surgery is advised in patients with left main disease or 3 vessel disease with left ventricular dysfunction.

Prognosis of unstable angina

About 10-30% patients of unstable angina develop an early myocardial infarction and one year mortality is 10-20%.

LONG -TERM RISK REDUCTION IN PATIENTS WITH UNSTABLE ANGINA

- Antiplatelet therapy: aspirin, clopidogrel.
- Beta- blockers.
- Blood pressure control.
- Cholesterol reducing drugs (statins).
- ACE inhibitors.
- Cessation of smoking
- Exercise and weight reduction.
- Low fat diet.

CLINICAL PRESENTATIONS OF CORONARY ARTERY DISEASE

Clinical presentation	Pathology
Stable angina	Ischemia due to fixed atheromatous stenosis of one or more coronary arteries.
Unstable angina	Ischemia caused by incomplete obstruction of coronary artery due to plaque rupture with superimposed thrombus formation and spasm.
Myocardial infarction	Ischemia caused by incomplete obstruction of coronary artery due to plaque rupture with superimposed thrombus formation causing myocardial necrosis.
Heart failure	Myocardial dysfunction due to infarction or ischemia
Arrhythmia	Altered conduction due to infarction or ischemia.
Sudden death	Ventricular arrhythmia, asystole or massive myocardial infarction.

MYOCARDIAL INFARCTION (MI)

Acute ischemic necrosis of an area of myocardium is known as myocardial infarction OR myocardial necrosis occurring as a result of critical imbalance between coronary blood supply and myocardial demand is called myocardial infarction. In majority of patients MI develops in left ventricle; right ventricular infarction frequently accompanies left ventricular inferior wall MI.

PREDISPOSING FACTORS

1. Myocardial infarction result from prolonged ischemia precipitated in most cases by formation of occlusive thrombus at the site of rupture of an athermatous plaque in coronary artery.
2. Rarely infarction may result from prolonged vasospasm, inadequate myocardial blood flow e.g. hypotension) or excessive metabolic demand.
3. Very rarely myocardial infarction may be caused by embolic occlusion, vasculitis, aortic root dissection, or aortitis.

PRECIPITATING FACTORS

1. Reduced myocardial perfusion due to hypotension as a result of hemorrhage or septic shock.
2. Increased myocardial oxygen demand secondary to aortic stenosis, fever and tachycardia.
3. Respiratory tract infections, hypoxemia of any cause, hypoglycemia, sympathomimetic drugs, allergy.

CIRCADIAN PERIODICITY

There is a marked circadian periodicity for the time of onset of myocardial infarction, with peak incidence of events between 6 AM and 12 noon. The early morning hours are associated with rise in plasma catecholamines and cortisol and increased platelet aggregability. It is also possible that immobility during sleep may cause aggregation of platelets and thrombus formation.

This is observed that the circadian periodicity is lost in patients taking beta-blocker or aspirin before their presentation with myocardial infarction.

CLINICAL FEATURES

Symptoms

Chest pain:
The pain is retrosternal similar to angina in location and radiation but it occurs at rest or with less activity and is more severe and lasts longer (> than 30 min). Pain may begin with exercise or psychological stress but may occur at rest without obvious precipitating factors. It is not relieved by nitroglycerine. Some patients note only dull ache or numbness of the wrists in association with severe retrosternal or precordial discomfort, pain may also begin in epigastrium and simulates abdominal disorders. Pain of angina and myocardial infarction is thought to arise from nerve endings in ischemic or injured but not necrotic myocardium. Pain often disappears suddenly and completely when blood flow to the infarct territory is restored (with thrombolytic therapy or angioplasty). In some patients especially elderly, MI manifests clinically not by chest pain but rather by symptoms of acute left ventricular failure (dyspnea), chest tightness or marked weakness or syncope.

Associated symptoms

- Nausea and vomiting are more common in inferior wall MI than in anterior wall MI.
- In some patients diarrhea or a violent urge to evacuate the bowels during acute phase of MI.
- Severe weakness, dizziness and palpitations may be associated with chest discomfort.
- There is profuse sweating which may drench the bed clothes.
- Syncope may develop due to fall in blood pressure or due to development of serious arrhythmia or heart block.
- Patient is restlessness due to anxiety and pain.
- There may be atypical presentation of MI with stroke or peripheral embolism, indigestion, acute mania or psychosis.

Painless or silent infarction: In minority of cases, pain is absent or minor and infarction is detected on routine ECG, (mostly in elderly, hypertensive and diabetic patients).

Sudden death:
About 20% of patients with acute infarction will die before reaching to hospital due to early arrhythmia (ventricular fibrillation).

On examination

General

Patient appears anxious, restless and in distress. They describe their pain with clenched fist held against the sternum. Profuse cold perspiration and pallor may be present due to sympathetic stimulation or left ventricular failure. Patient may present with cardiogenic shock. Patient may be confused or disoriented due to cerebral hypoperfusion.

Pulse:

1. Tachycardia: Due to anxiety, low cardiac output or arrhythmias.
2. Bradycardia: If there is inferior wall infarction.

Blood pressure:

1. There may be hypertensive response (>160/90 mmHg) in previous normotensive in the first few hours secondary to adrenergic stimulation due to pain, anxiety and agitation.
2. Previously hypertensive patients may become normotensive after MI or remain hypertensive.
3. Blood pressure may be low due to:
   - Dehydration (as a result of vomiting)
   - Medications such as nitrates, morphine and beta-blockers.
   - Left ventricular dysfunction.

Temperature

Majority of patients with MI develop fever within 24-48 hours as a nonspecific response to tissue necrosis that resolves by fourth or fifth day.

Respiratory rate

Respiratory rate may be increased due to anxiety, pain or heart failure.

Examination of precordium

Cardiac examination may be normal or having the following abnormalities:

- A soft first heart sound.
- Fourth heart sound.
- Third heart sound reflects left ventricular dysfunction.
- A transient systolic murmur due to mitral regurgitation due to papillary muscle dysfunction or left ventricular dilatation.
- Pericardial rub (pericardial rub is usually heard on the second or third day).

Lungs:

- Basal crepitations mostly present and do not necessarily indicate heart failure.
- Crepitations may be severe involving more than half of lung field due to left ventricular failure.
- Diffuse wheezing (rhonchi) may be present in severe left ventricular failure.

PHYSICAL SIGNS OF MYOCARDIAL INFARCTION

- **Signs of sympathetic activation**
  Pallor, sweating, tachycardia
- **Signs of vagal activation**
  Vomiting, sometimes bradycardia
- **Signs of impaired myocardial function**
  - Raised JVP
  - Narrow pulse pressure
  - 3rd heart sound
  - Quiet 1st heart sound
  - Diffuse apical impulse
  - Hyotension, oliguria, cold peripheries
  - Lung crepitations
- **Signs of tissue damage**
  - Fever
- **Complications**
  - Arrhythmias
  - Murmur of ventricular septal defect, mitral regurgitation
  - Pericardial rub.

INVESTIGATIONS

According to the WHO criteria myocardial infarction can be diagnosed, if two of the following three factors are present:

- A history of ischemic type chest pain.
- ECG changes of myocardial infarction.
- Initially a rise and then fall of cardiac enzymes.

ECG:

The classical evolution of ECG changes is myocardial infarction are:

Peaked (hyperacute) T waves → ST segment elevation → Formation of Q waves → T wave inversion.

These changes may occur over a few hours to several days. Occasionally initial ECG is normal and diagnostic changes appear a few hours later, therefore serial ECGs increase the yield of diagnosis. Interpretation of ECG becomes difficult when there is a bundle branch block or previous myocardial infarction.

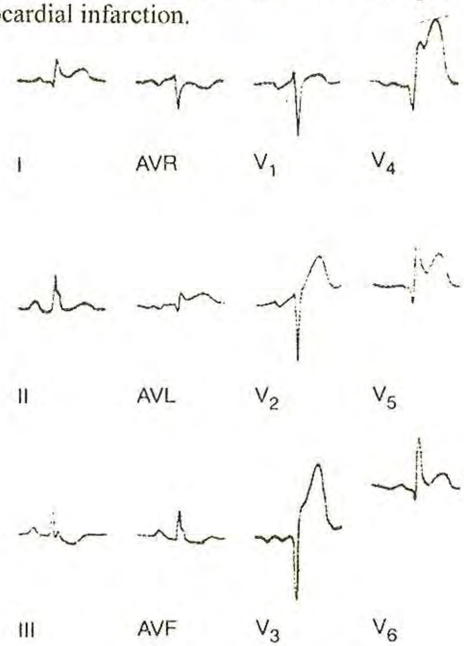


Fig. 13.64 **An acute anterolateral myocardial infarction** shown by a 12-lead ECG. Note the ST segment elevation in leads I, AVL, and V_2–V_6. The T wave is inverted in leads I, AVL and V_3–V_6. Pathological Q waves are seen in leads V_2–V_6.

ECG LOCALIZATION OF MYOCARDIAL INFARCTION		
Infarct location	**Leads showing changes**	**Likely coronary artery involved**
Inferior wall MI	II, III, aVF	RCA
Septal MI	V1-V2	LAD
Anterior wall MI	V3-V4	LAD
Anteroseptal	V1-V4	LAD
Extensive anterior wall MI	I, aVL, V1-V6	LAD
Lateral wall Mi	I, aVL, V5-V6	Circumflex
High lateral wall MI	I, aVL	Circumflex
Posterior wall MI	Prominent R in V1	RCA or Circ
Right ventricular MI	ST elevation in V1 and right –sided V4 with inferior wall MI	RCA

LAD: left anterior descending artery Circ: circumflex artery
RCA: right coronary artery

TYPES OF INFARCTION

On the basis of their associated ECG findings, acute myocardial infarction can be divided into two groups:

Q-wave infarction (transmural infarction)

In this type of myocardial infarction pathological Q-waves develop on ECG. These infarctions result from complete thrombotic occlusion of coronary artery and manifest on ECG by symmetrically peaked T waves replaced after several minutes by ST-segment elevation.

Non-Q wave infarction

It is also called Non- ST elevation infarction (NSTEMI) and Subendocardial infarction.

Non- Q wave or non- ST elevation MI develops from high-grade but non-occlusive thrombi (obstruction of coronary artery is not complete). This infarction is associated with ST-segment depression and / or T wave inversion without evolution of pathologic Q waves. There is also some loss of R waves in leads facing the infarct.

Significance

This division of Q wave and non-Q wave myocardial infarction has pathophysiologic and prognostic importance. Patients with Q-wave infarctions in general have a larger area of myocardium at risk and have a higher in-hospital mortality rate than patients with non-Q wave infarctions; however, over the course of the year after an infarction, the mortality of non-Q wave infarction increases, approaching that of Q-wave infarction. Therefore we can say that initial mortality of Q-wave infarction is higher than in non-Q wave infarction and prognosis of non-Q wave infarction is better at the time of infarction.

CARDIAC ENZYMES

Myocardial infarction leads to detectable rise in the plasma concentration of enzymes normally confined within cardiac cells. The enzymes most widely used in the detection of myocardial infarction are the following:

Cardiac specific troponins

Troponin T and troponin I: These enzymes are highly specific to cardiac injury and can detect small infarctions that are below the detection limit for CK-MB. Troponin T and I rise early (within 2 – 4 hours) and remains elevated (troponin I, 7 – 10 days and troponin T, 10-14 days). Therefore these

enzymes are especially helpful if a patient comes 2-3 days after infarction because CK-MB returns to normal till that time while these enzymes remain elevated. Although LDH is also elevated for 10 days but it is non-specific and is also elevated in other conditions, this is why troponin T or I is preferred. Troponin T kits are available in the market and this test can be performed at bedside. It is now most widely used test for cardiac marker.

Creatine Kinase (CK)

It rises within 4 – 8 hours, peaks at 24 hours and generally returns to normal by 2-3 days.

Creatine kinase has three isoenzymes
CK – MB – Present in heart.
CK – MM – Present in skeletal muscles
CK – BB – Present in brain

Therefore CK may be falsely positive in muscle disease, alcohol intoxication, diabetes, skeletal muscle trauma, exercise, convulsions, intramuscular injections and pulmonary embolism.

CK – MB is more specific and is performed to detect myocardial necrosis. Serial elevation and decline is more important for the diagnosis of myocardial infarction than measurement at a single point because CK-MB may also be elevated in cardiac surgery, myocarditis and electrical cardioversion.

Serum myoglobin

Myoglobin released from injured myocardium comes into circulation quite early and is very sensitive for detection of infarction (1-4 hours), however it is not very specific because minor skeletal muscle trauma also releases myoglobin. In patients presenting less than 6 hours of symptoms onset and with ST elevation in whom the diagnosis of MI is in doubt, an elevated myoglobin level is associated with an increased risk of mortality.

OTHER SERUM MARKERS

Before availability of troponins several other markers were used for confirmation of MI, they were non-specific and usually not performed now except in government hospitals laboratories and in small centers. You must be aware of these markers because in **viva exam** you may be asked to interpret the report of cardiac enzymes.

1. **Asparate aminotransferase (AST)** also called serum glutamic oxaloacetic transaminase (SGOT).
   It peaks at 24-48 hours and may fall to normal by 72 hours. It is nonspecific to heart and may also be released by damaged RBCs, kidney, liver and lung.

2. **Lactate dehydrogenase (LDH)**
   It peaks at 3-4 days and remains elevated for 10-14 days (important for the diagnosis of MI in patients presenting after few days of MI).
   It is also nonspecific and is also released from damaged liver, skeletal muscles, and red blood cells.

Blood CP / ESR

- Polymorphonuclear leucocytosis
- Raised ESR

X-ray chest

- It may demonstrate pulmonary edema
- Heart size is usually normal
- Enlarged cardiac shadow indicates CCF or pericardial effusion.

Echocardiography

Echocardiography provides convenient bedside assessment of left ventricular global and regional function. This may be helpful in diagnosis and management of infarction. Normal wall motion makes an infarction unlikely.

Radionuclide scan

Technetium-99 pyrophosphate scan can be used to diagnose acute myocardial infarction; it is performed in patients in whom the diagnosis by ECG and enzymes is not possible because patient represents several days after infarction or there is intra-operative infarction.

ESTIMATION OF INFARCT SIZE

Quantity of myocardium infracted has important prognostic value, therefore estimation of infarct size should be done to predict the prognosis and to work for minimizing the size of infarct.

ECG

- More the number of ECG leads showing ST-segment elevation, larger is the infarct size and higher is the mortality.
- Higher is the ST elevation, extensive is the MI and higher is the mortality.

Cardiac enzymes

Higher is the quantity of CK and CK-MB, larger is the infarct and higher is the mortality.

Echocardiography

Larger the area with wall motion abnormality, larger is the infarct.

MANAGEMENT

All patients with suspected myocardial infarction should be confined to strict bed rest and admitted in hospital preferably in CCU.

General measures

1. **Activity:** Complete bed rest for the first 12 hours, then sitting upright or in a chair within 24 hours, if no hypotension patient is allowed to ambulate in his room or shower himself on third day. By day 4-5 after MI progressively increased ambulation to a goal of 600 feet at least 3 times daily.
2. **Diet**: Nothing by mouth or clear liquids by mouth for the first 4-12 hours because there is risk of vomiting and aspiration.
3. **Bowel:** A bedside commode facility should be available. Give laxative if there is constipation.
4. **Sedation** for anxiety such as alprazolam (Xanax 0.5 mg).
5. **Oxygen** supplementation, if oxygen saturation is low.

Specific

Pain relief

- Control of cardiac pain is typically accomplished with combination of nitrates, morphine, oxygen and beta-blockers.
- Intravenous cannula should be inserted and powerful analgesic is given such as morphine 4-8 mg plus cyclizine (Marzine 50 mg) I/V. subsequent small doses (2-8mg) can be given every 5-15 minutes until the pain is relieved or there is evidence of morphine toxicity such as hypotension, respiratory depression or severe vomiting.
- Morphine relieves pain and anxiety. If morphine causes hypotension or bradycardia give atropine 0.5-1.5mg IV and for respiratory depression naloxone 0.1-0.2mg IV as an antidote.
- Intramuscular injection should be avoided in patients with MI because painful hematoma may develop from following thrombolytic therapy.

Aspirin

First tablet of Aspirin (300mg) should be given in a soluble or chewable form to achieve therapeutic blood levels rapidly through buccal absorption rather than absorption through the gastric mucosa. Then give 75-300 mg daily. Aspirin causes 30% reduction in short-term mortality on its own and enhances the effect of thrombolytic therapy.

Nitrates:

- Unless contraindicated sublingual nitroglycerine (Angised) should be given to relieve chest discomfort. After first tablet monitor the response, if no hypotension or bradycardia further tablets may be given.
- Nitroglycerine must be given cautiously in inferior wall MI (as there may be associated right ventricular infarction in which nitrates should be avoided because patient may become severely hypotensive in response to nitroglycerine). Nitrates should also not be used if patient is hypotensive (systolic BP <90 mmHg).
- Intravenous nitroglycerine is not used in all patients of MI because recent trials show no survival benefit from routine use of nitrates after MI. Following are the patients in which IV nitrates are used for the first 24-48 hours:
  - Left ventricular failure due to MI.
  - Patient with hypertension.
  - Recurrent or persistent ischemic pain.
  - High-risk patient especially with large anterior wall MI.

- There is no benefit of empirical long- term use of oral or cutaneous nitrates beyond the first 48 hours of MI in asymptomatic patients and not advised unless angina or left ventricular failure is present.
- Nitroglycerine (Isoket) start infusion at the rate of 5-10 mg/min with increases of 5-20 mg/min until the mean arterial BP is reduced by 10% of its baseline level in normotensive patients and by 30% for hypertensive patients, but in no case below systolic BP <90mmHg.

Beta-blockers

Acute beta-blockade reduces the risk of cardiac rupture, decreases ischemic chest pain and infarct size. It also reduces the incidence of ventricular arrhythmias. Metoprolol (Lopressor 5 mg) IV every 5 minutes for 3 doses provided the heart rate does not fall below 60 beats/min and the systolic BP does not drop below 100mmHg. Then oral maintenance dose is started with metoprolol (Tab. Mepressor) 50 mg every 6 hours for 2 days and then 100mg twice daily. Early use of beta- blocker is associated with a 15% reduction in mortality and re-infarction. Beta- blockers should be avoided in cardiac failure, heart block, bronchospasm or severe bradycardia.

Angiotensin – Converting Enzymes Inhibitors

They prevent or at least reduce the left ventricular dilatation and cardiac failure following mayocardial infarction and should be given to all patients who are hemodynamically stable (systolic BP 100 mmHg) within first 24 hours and continue in high risk patients of MI for the whole life, In non- high risk patients ACE inhibitors may be discontinued. High risk patients are with CCF, large regional wall motion abnormality or evidence of reduced generalized LV function.

The benefits are greatest in patients with low ejection fractions (ejection fraction <40%), large infarctions and with heart failure.

- Captropil (Tab. Capoten 25 mg) initial dose 6.25 mg then increase every 6-8 hours to a maximum of 50 mg 3-times daily as long as the systolic BP is >90-100 mmHg.

Thrombolytic therapy

Coronary thrombolysis helps in restoring coronary artery patency, limits infarct size, preserves left ventricular function and improves survival. The greatest beneficial effect occurs if treatment is initiated within first 1-3 hours, when a 50% or greater reduction in mortality rate can be achieved.

Thrombolytic drugs should be given to all patients presenting within 12 hours of onset of major symptoms and ST-segment elevation or with new LBBB provided there is no contraindication.

The benefit is greatest in patients with large infarcts i.e. those with anterior wall infarcts, also in inferior wall infarct. Non- Q wave infarct are usually not benefited. Thrombolytic therapy is also not effective in patients with prior bypass surgery because it is ineffective in opening the bypass grafts. Therefore thrombolytic therapy is only given to patient presenting with ST – segment elevation MI. Reperfusion rate after thrombolytic therapy is about 65%. Reperfusion is unsuccessful in about 25% of patients and early re-occlusion occurs in further 10%.

- Thrombolytic therapy is given to patients of ST elevation MI or new left bundle branch block who are under 75 years of age and present within 6-12 hours of the onset of the symptoms.

Streptokinase

Streptokinase: 1.5 million units in 100 ml of saline I/V over 1 hour. There is no need to give heparin with streptokinase. Successful reperfusion is recognized by:

- Abrupt cessation of pain.
- ST- segment resolution
- The occurrence of ventricular arrhythmia (idioventricular rhythm).
- Rapid evolution of Q-waves on ECG
- An early peak of CK (by 12 hours).

Advantage

Streptokinase is relatively cheap (about Rs. 5500).

Disadvantages

- More likely to cause allergic reactions such as fever, chills, rashes, and anaphylaxis.
- It is antigenic, produces antibodies against it and therefore should be avoided if patient has received it previously because it will be ineffective. However if thrombolytic therapy is required in future , another agent may be used. Streptokinase may be used again for next MI within 6 days and after one years year. Recent infection with streptococci or previous

- administration of streptokinase (within one year) induces antistreptokinase antibodies, which may cause allergic reaction or resistance to the fibrinolytic effect of streptokinase.
- It can cause severe hypotension if given rapidly.

Altepase or recombinant tissue plasminogen activator (t-PA).

It is given as a 15-mg bolus followed by 50 mg over next 30 minutes and then 35 mg over the following 60 minutes. Intravenous heparin is also recommended for at least 24-hours.

Advantages

- It is not antigenic and can be given next time.
- It does not cause hypotension.
- It does not cause allergic reaction.

Disadvantages

It is about 10-times more expensive than streptokinase. Therefore it should be used if stretokinase is contraindicated due to allergy, previous exposure or profound hyotension.
It is associated more with intracranial hemorrhage in patients over 70 years or with elevated blood pressure.

Other thrombolytic drugs

- Reteplase
- Tenecteplase (TNK-tPA)

Complications of thrombolytic therapy

- Bleeding e.g. intracranial hemorrhage
- Resistance to streptokinase if given again within one year or streptococcal infection within one year.
- Splenic rupture, aortic dissection and cholesterol embolization is also reported.

Anti-coagulants

After thrombolytic therapy aspirin should be continued and anticoagulation with intravenous heparin is also continued for at least 24-hours after tPA but not recommended in patients receiving streptokinase. When given heparin 5000 units IV bolus followed by 1000 units per hour IV infusion. Low molecular weight heparin may be used instead of unfractioned heparin.

Patients who do not receive thrombolytic therapy should be given 7500 units of heparin S/C 12-hourly until the patient is ambulatory to prevent thromboembolism.

CONTRAINDICATIONS TO THROMBOLYTIC THERAPY

Absolute contraindications

- Bleeding disorder (an active internal bleeding)
- Previous subarachnoid or intracerebral hemorrhage.
- Non-hemorrhagic stroke within the past year.
- Recent trauma (including traumatic resuscitation).
- Recent surgery o the head or spine.
- Severe hypertension systolic > 180mmHg or diastolic > 110 mmHg.
- Pregnancy.
- Prolonged CPR (>5-10min)

Relative contraindications

- Recent major thoracoabdominal surgery or biopsies.
- Current use of anticoagulants (INR > 2-3).
- High probability of active peptic ulcer.
- Endocarditis
- Severe diabetic proliferative retinopathy.

➢ Older patients have greater complications of thrombolytic therapy but also get potentially greater benefit, therefore old age is not a contraindication.

Primary percutaneous coronary intervention (primary PCI)

Immediate or primary angioplasty is safer alternative to thrombolytic therapy. It is the approach of choice in patients with cardiogenic shock or absolute or many relative contraindications to thrombolytic therapy. However it should be performed very early (within 60 min) in experienced and high volume centers. Patency rates of primary angioplasty are 85-90% (while 65% in thrombolytic therapy). Glycoprotein IIb/IIIa inhibitors are used during and after procedure.

MANAGEMENT OF MYOCARDIAL INFARCTION

1. An I/V cannula is inserted for emergency medication.
2. Morhine. 4-8 mg I/V + cyclizine 50mg I/V to relieve pain.
3. Oral aspirin 1 tablet chewable.
4. Nitroglycerine (Angised) sublingually if blood pressure is stable.
5. Oxygen if saturation is low.
6. Intravenous beta-blocker (Lopressor) if tachycardia.
7. Thrombolytic streptokinase 1.5 million units over 1 hour.
8. Acute angioplasty (primary percutaneous intervention PCI) if thrombolytic therapy is contraindicated.
9. Isosorbide dinitrate or nitroglycerine for 24-48 hours to relieve persistent pain if blood pressure is stable.
10. Watch for ventricular fibrillation daily and defibrillate if needed.
11. Alprazolam (Xanax) – to relieve anxiety.
12. Bed rest for first 24-48 hours with bedside commode facility. Smoking should not be allowed.

INDICATIONS OF REVASCULARIZATION AFTER MI

Following patients are likely to get benefit from early angiography and revascularization either in the form of angioplasty or bypass surgery.

- Patients received thrombolytic therapy but have residual symptoms or laboratory evidence of ischemia.
- Patients with left ventricular dysfunction (ejection fraction <30-40%) and evidence of ischemia.
- Patients with non-Q wave MI and evidence of more than a mild ischemia.
- Patients with markedly positive exercise test and multivessel disease

FOLLOW UP TREATMENT & SECONDARY PREVENTION

If a patient has no complication during hospital stay he may be discharged in 3-5 days. He has no significant ventricular arrhythmia, recurrent ischemia or CCF during hospitalization. Hospital stay may be prolonged for patients with complications until their condition has been stable for several days. Patients should receive the following instruction before discharge from the hospital:

1. Initially ambulation limited to home.
2. No lifting heavy weights
3. Stop smoking.
4. Reduce weight.
5. Control blood pressure.
6. Gradually increased activity, cardiac rehabilitation, and exercise training after 4-8 weeks.
7. Submaximal ETT or Persantin thallium scan before discharge (after 3-5 days of uncomplicated MI) or maximal test after 6-8 weeks can predict the subsequent outcome.
8. Sexual intercourse after 6 weeks.
9. Returning to work after 6-8 weeks.
10. Strict sugar control in diabetics.
11. LDL cholesterol should be lowered below 100 mg/dl with lipid lowering drugs such as statins (simvastatin, atrovastatin).
12. Aspirin continue indefinitely.
13. Beta-blocker has been shown to reduce the incidence of death in six months following an acute myocardial infarction. One of the beta-blockers e.g.
    - Metoprolol 50 mg twice daily
    - Atenolol 100 mg once daily.

10. ACE inhibitors: prevent progressive left ventricular dilatation and dysfunction.

11. **Air travel:** air travel should be avoided for 3 weeks after MI even the patient is asymptomatic. A negative ETT is desirable. Unstable postinfarction patient should not fly. Post angioplasty or bypass operation patient should not fly until stable and at least 2 weeks after procedure.

RISK STRATIFICATION AFTER MI

High - risk patients after myocardial infarction in which mortality is high

History and examination

1. Age greater than 70 years
2. Female gender
3. History of diabetes mellitus, hypertension and non-cardiac vascular disease
4. Prior angina pectoris
5. Previous myocardial infarction
6. Severity of left ventricular dysfunction
7. Postinfarction angina re- infarction
8. Increased heart rate
9. Low systolic blood pressure
10. Signs of left ventricular failure such as low BP, tachycardia, S3 gallop, peripheral hypoperfusion and pulmonary congestion.
11. Mitral regurgitation or VSD as a complication of MI.

ECG

1. Location of MI; mortality is two times higher after anterior wall MI than after inferior wall MI.
2. Mortality is higher if there is ***right*** ventricular infarction with inferior wall MI than in inferior wall MI without right ventricular infarction.
3. Increased number of ECG leads showing ST elevation higher is the mortality.
4. More is the ST elevation higher is the mortality
5. Type II second degree or third degree heart block
6. Bifascicular or trifascicular block
7. Reciprocal ST depression of anterior leads in inferior wall MI.
8. Atrial fibrillation

LABS

Higher the level of cardiac enzymes greater is the mortality.

ECHO

1. Ejection frction < 40% is associated with increased risk of death.
2. Hypokinesia detected within 12 hours of onset of symptoms identifies the patient at increased risk of pump failure, arrhythmias and death.

COMPLICATIONS OF MYOCARDIAL INFARCTION

Early complications within first 2-3 days

1. Cardiac arrhythmias
2. Cardiac failure
3. Pericarditis

Later complications

1. Recurrent infarction
2. Angina
3. Thromboembolism
4. Mitral valve regurgitation after 3-5 days)
5. Ventricular septal defect, cardiac rupture (after 3-5 days).

Late complications

1. Post-myocardial infarction syndrome
2. Shoulder-hand syndrome
3. Ventricular aneurysm
4. Recurrent cardiac arrythmias

CARDIAC ARRHYTHMIAS

- Sinus bradycardia
- Sinus tachycardia
- Atrial fibrillation
- Atrial flutter
- Ventricular ectopics
- Ventricular tachycardia
- Ventricular fibrillation
- Conduction abnormalities and Heart block

Sinus bradycardia

- Sinus bradycardia occurs in 16% to 25% of patients with acute myocardial infarction, particularly of the inferior or posterior wall.
- It is most often transient, resulting from an increase in vagal tone.
- No specific therapy is needed for asymptomatic sinus bradycardia.
- If symptoms of hemodynamic compromise (hypotension) or ischemia occur, intravenous atropine sulfate, 0.6 to 1 mg, is usually effective. Persistent bradycardia warrants consideration of temporary pacing, which also may be necessary if the patient requires therapy with drugs that may further depress sinus node automaticity, particularly beta blockers. Since sinus bradycardia usually resolves, long-term pacing is rarely needed.

Sinus tachycardia

About 30% patients experience sinus tachycardia after MI. Sinus tachycardia develops due to sympathetic overactivity resulting from anxiety, persistent pain, left ventricular failure, fever, pericarditis, hypovolemia (resulting from poor intake, vomiting, vasodilators or diuretic use), pulmonary embolism, use of atropine or dopamine.

Sinus tachycardia increases myocardial oxygen demand therefore intensifying ischemia or infarction. Usually no specific treatment is needed. If there is no cardiac failure or hypovolemia then beta- blocker may be given while correcting the underlying cause.

Atrial fibrillation (AF)

Atrial fibrillation is seen in 10% to 15% of patients with myocardial infarction, most commonly in those who have significant left ventricular dysfunction and CHF. It also results from atrial irritation caused by pericarditis and atrial ischemia or infarction. The presence of atrial fibrillation in patients with myocardial infarction increases mortality during and after hospitalization. This increase is due not to the arrhythmia itself but to factors associated with it, particularly left ventricular dysfunction, CHF, and cardiogenic shock .

Initial treatment of atrial fibrillation depends on the clinical situation and associated symptoms. Often, the arrhythmia is only transient and requires no therapy; even when persistent, it generally responds to appropriate treatment. Heparin therapy should be initiated soon after onset of atrial fibrillation, because anticoagulation reduces the small risk of embolism and eliminates concern about reversion within 48 hours.

Management

Control of heart rate

Prompt control of the heart rate is essential; an AV nodal blocking agent should be given intravenously--preferably a beta blocker or, if contraindicated, verapamil hydrochloride (Isoptin) or diltiazem hydrochloride. Digoxin is not likely to slow the heart rate promptly but may be of use when atrial fibrillation is due to CHF, since digoxin therapy improves left ventricular function and hemodynamics and may result in reversion of atrial fibrillation and restoration of normal sinus rhythm.

- Metoprolol (Lopressor) 2.5-5mg/hour if cardiac function is adequate (i.e. no heart failure), verapamil (Isoptin) if beta blockers are contraindicated.
- Digoxin: if heart failure is present with atrial fibrillation (0.5 mg IV as initial dose, then 0.25 mg IV every 90-120 min---- up to 1-1.25 mg for loading dose followed by 0.25 mg daily).

Electric cardioversion to restore sinus rhythm is indicated in patients with severe hemodynamic compromise or refractory symptoms of ischemia due to atrial fibrillation. Electrical cardioversion (100 J for atrial flutter and 200 J for atrial fibrillation) if patient is hemodynamically unstable and develops hypotension, heart failure or ischemia.

Pharmacological cardioversion

When atrial fibrillation persists, reversion with antiarrhythmic therapy should be attempted.

Amiodarone hydrochloride (Cordarone) is very effective for atrial fibrillation and is not associated with increased mortality in patients with myocardial infarction. (150 mg IV bolus then 15-30 mg/h IV).

Ibutilide: Although intravenous ibutilide fumarate has been beneficial for reverting new onset atrial fibrillation in about 30% to 40% of patients, its efficacy and safety in patients with myocardial infarction have not been well studied. Its major side effect is torsades de pointes; whether patients who have had a recent myocardial infarction are at increased risk for this complication is uncertain.

Sotalol hydrochloride, a drug with class III and beta-blocking activity, is an appropriate first-line agent, since it may prevent atrial fibrillation in patients with myocardial infarction and is safe in this setting.

In patients in whom the use of any antiarrhythmic drug is a concern, a reasonable approach is maintenance of atrial fibrillation with the use of an AV nodal blocking drug (especially a beta blocker) and long-term anticoagulation with warfarin sodium.

Atrial-flutter

Atrial flutter is not commonly seen in patients with myocardial infarction, and after reversion it is not likely to recur . As with atrial fibrillation, the first step in management is to slow the heart rate, which can often be achieved with an AV nodal blocking agent. If this is not possible or if atrial flutter is accompanied by symptoms, electric cardioversion is highly effective. An alternative therapy, particularly for asymptomatic atrial flutter, is intravenous ibutilide, which is effective in reverting atrial flutter and restoring sinus rhythm in about 60% of patients.

Since atrial flutter is not likely to recur, long-term suppression is unnecessary. However, if atrial flutter does recur and is accompanied by symptoms, long-term suppressive therapy is indicated with class III agents. Use of radiofrequency catheter ablation, which is an effective approach for the prevention and possible cure of atrial flutter, is increasing. However, its use and role in patients with a recent myocardial infarction have not been evaluated.

Supraventricular tachycardia (SVT)

- Hypoxia and electrolyte imbalance should be corrected.
- Adenosine(Adenocor 6mg) 6-12 mg IV bolus, if no response or recurrence then give verapamil (Isoptin) 5-10mg IV bolus.
- Electrical cardioversion if no response to adenosine. Verapamil, diltiazem or digoxin for maintenance therapy.

Ventricular ectopics (Premature ventricular contractions (PVCs).

Ventricular ectopics commonly occur after myocardial infarction. Previously it was believed that their occurrence precedes the development of ventricular fibrillation if they are frequent (more than 5 per minute), multiform (different shapes) or R on T (falling on the peak of the preceding T wave). Now this is clear that these PVCs may be present in patients who do not develop ventricular fibrillation and ventricular fibrillation develops frequently without prior PVCs and develops in spite of suppression of these PVCs.

Treatment with anti-arrhythmic drugs has not been shown to reduce likelihood of subsequent ventricular tachycardia or fibrillation. Therefore instead of suppressing PVCs try to find out whether there is recurrent ischemia, metabolic or electrolyte imbalance. Moreover early administration of beta- blocker is effective in reducing the incidence of ventricular fibrillation in cases of myocardial infarction.

- PVCs after MI require no treatment; find out the cause such as sympathetic overactivity (tachycardia), ischemia, metabolic or electrolyte imbalance.

Ventricular tachycardia (VT)

It may lead to ventricular fibrillation, therefore should be treated. Hypokalemia increases the risk of ventricular tachycardia, therefore identify hypokalemia early in MI patient and maintain potassium level above 4.5 mEq/liter

- If the patient is hemodynamically stable, give lignocaine 1mg/kg iv bolus. A 2mg/min drip is started concurrently. Additional boluses of 0.5 mg/kg every 8-12 min to maximum dose of 3 mg/kg may be given if arrhythmia persists. If not responding then amiodarone (Cordarone) 150mg over 10 minutes followed by 360mg over next 6 hours and then 540 mg over 18 hours followed by an infusion of 20-80 mg/kg/min. Continue maintenance infusion for several days. Hypotension and cardiac failure may be induced by acute use of amiodarone because of its negative inotropic effect.
- If patient is hemodynamically unstable (BPless, pulseless) then electrical cardioversion (100-200 J) should be performed.
- After reversion to sinus rhythm correct the underlying abnormalities such as hypoxia, hypotension, acid- base or electrolyte disturbance.
- Recurrent or refractory ventricular tachycardia requires Implantable Cardioverter Defibrillator (ICD). Urgent angioplasty or bypass surgery may help control the refractory ventricular tachycardia.

Ventricular fibrillation (VF)

It occurs in 5-10% of patients in hospital. The risk is much higher in the first hour after infarction, and it is thought to be the major cause of death before reaching hospital. There are two types of ventricular fibrillation.

2. *Primary:* Ventricular fibrillation occuring suddenly and unexpectedly in first few hours following MI in the absence of signs of severe cardiac failure or cardiogenic shock is called primary ventricular fibrillation. It is treated with unsynchronized electrical countershock (200-360 J). Ventricular fibrillation refractory to electric shock may be more responsive after treatment with adrenaline 1 mg IV or amiodarone 75-150mg IV bolus. Then defibrillate again. Recurrence of ventricular fibrillation can be treated with Lignocaine or amiodarone I/V infusion. Serum potassium should be above 4.5 mEq/liter.
3. *Secondary:* Ventricular fibrillation developing late after 48 hours of MI and occurring in patients with large infarcts and left ventricular dysfunction is called secondary ventricular fibrillation. It is also treated with defibrillator but prognosis is poor.

Heart block

Heart block with inferior wall MI

Heart block is common and occurs in approximately 20% of inferior wall MI as a result of increased vagal tone and release of adenosine and is usually transient.

1. First degree heart block does not need treatment
2. Second degree is often Mobitz type 1 and requires treatment only if associated with hypotension, dyspnea or chest pain due to very slow heart rate.
3. Complete heart block with inferior wall MI rarely requires pacemaker because there is generally a satisfactory escaper rhythm maintaining adequate heart rate. Complete heart block may need treatment with atropine, if escape rhythm is wide or patient develops hypotension due to low cardiac output then temporary pacemaker (TPM) insertion is required. Heart block resolves within a few days and permanent pacemaker is required if heart block persists more than 2 weeks.

Heart block with anterior wall MI

Heart block in anterior wall MI has very different significance from that occurs with inferior wall MI. It indicates extensive damage of His-Purkinje system and bundle branches due to myocardial necrosis and carries poor prognosis.

- First- degree heart block in anterior wall MI is unusual.
- Mobitz type II or complete heart block need urgent temporary pacemaker, however morbidity and mortality is high due to extensive myocardial damage.
- Patients with anterior wall infarction who progress to second or third degree heart block should be considered for insertion of a prophylactic permanent pacemaker (PPM) before discharge.

Bundle branch block

- Conduction disturbance in anterior wall MI is generally right bundle branch block (RBBB). It can progress to complete heart block. RBBB is associated with increased mortality if accompanied by congestive heart failure.
- Left bundle branch block is most often a chronic manifestation of hypertension and myocardial dysfunction rather than an acute abnormality, however it may be acute with MI.
- Observe the patient of bundle branch block for progression to complete heart block that requires insertion of temporary pacemaker.

Bifascicular block

RBBB with either left anterior or posterior fascicle block is called bifascicular block. It increases the risk of progression to complete heart block resulting in increased mortality. Bifascicular block with prolonged PR interval indicates trifascicular block.

- Alternating bundle branch block (right and left), bifascicular block, or trifascicular block require temporary pacemaker.

INDICATIONS OF TEMPORARY PACEMAKER INSERTION AFTER MI

- Mobitz II second degree heart block
- Bifascicular block
- Trifascicular block
- LBBB with first degree AV block
- Alternating right and left bundle branch block
- Complete heart block

POST-MI ANGINA

Post- infarct angina occurs up to 50% of patients. Most have a residual stenosis in the infarct- related vessel. Patient should be treated as a case of unstable angina with intravenous heparin and nitrates. Early coronary angiography and angioplasty should be considered.

MECHANICAL COMPLICATIONS

These complications occur in both anterior and inferior wall MI usually 3-7 days after the acute event. They are usually associated with pulmonary edema. Diagnosis is on echocardiography. Treatment is surgical, circulation should at first be supported by intra- aortic balloon counterpulsation, dopamine, dobutamine in combination with vasodilator such as nitroprusside.

- **Mitral regurgitation:** Papillary muscle damage may cause severe mitral regurgitation presenting with holosystolic murmur and severe heart failure.
- **Ventricular septal defect:** Rupture of interventricular septum may cause left to right shunting through VSD. Characteristically, the patient suddenly deteriorates accompanied by the development of a pansystolic murmur, maximal at left lower sternal border. Patient presents with biventricular failure that frequently leads to cardiogenic shock. Prompt surgery is required.
- **Cardiac rupture:** Rupture of the ventricle may lead to cardiac temponade and is usually fatal.

ACUTE LEFT VENTRICULAR FAILURE

Large myocardial infarction may lead to severe cardiac failure while mild failure may occur in about 40% of cases. Nitrates, diuretics and ACE inhibitors are required for treatment. For inotropic support dobutamine started at 2.5 μg/kg/min may be increased up to 15-20 μg/kg/min at 5-10 min intervals. Dopamine is combined when there is hypotension because it causes peripheral vasoconstriction. Digoxin is not effective for acute heart failure.

Killip (clinical) classification of heart failure in patients with acute myocardial infarction.

Class	Description	Incidence %	Mortality %
I	No heart failure	40	5
II	Mild left ventricular failure (few basal crepts, S3, upper lobe diversion on chest X-ray)	40	20
III	Pulmonary edema	10	40
IV	Cardiogenic shock	10	90

HYPOTENSION AND CARDIOGENIC SHOCK

- Patient with hypotension BP < 100mmHg and signs of hypoperfusion should be hemodynamically monitored.
- Hypotension after MI may be due to hypovolemia, drugs, pericardiac temponade, or right ventricular infarction.
- Most patients with hypotension will have moderate to severe left ventricular dysfunction 20% of LV is infracted, while > 40% in cardiogenic shock.
- Dopamine is the drug of choice for cardiogenic hypotension; at low dose (< 5 µg/kg/min) it improves renal blood flow, at intermediate dosage (2.5-10 µg/kg/min) it stimulates myocardial contractility, at higher dosage (>8 µg/kg/min) it is a potent alpha- adrenergic agonist. Dopamine is usually combined with dobutamine.
- Patients with cardiogenic shock has bad prognosis, with 30 days mortality rate 50-80%. Early intervention by angioplasty or CABG offers the best chance of survival.

LEFT VENTRICULAR THROMBUS AND ARTERIAL EMBOLISM

Left ventricular mural thrombus may form on the endothelial surface of the infracted region, such thrombus is dislodged, forming a systemic embolus. Diagnosis is made with echocardiography. Features on echo that suggest increased risk of detachment of thrombus are increased mobility and protrusion into the ventricular chamber, visualization in multiple views and contiguous zones of akinesia and hyperkinesias. Embolism may involve any artery but commonly causes stroke or lower limb ischemia with severe leg pain.

Management

Anticoagulation therapy protects from embolism initially with heparin to elevate the aPTT to 1.5-2 times of control and then with warfarin for 3-6 months, lower limb embolism requires surgical removal of clot.

PERICARDITIS:

This is characterized by sharp chest pain and pericardial rub. It is frequently occurs in the first few days after an acute MI especially following anterior wall infarction. Characteristically pericarditic pain varies with inspiration and with body posture—worse on inspiration and alleviated by sitting up and leaning forward. There may be a pericardial friction rub.

ECG

ECG shows generalized ST segment elevation (concave upward) with peaked T waves.

Management:

Aspirin and paracetamol are usually effective. NSAIDs and anticoagulants should be avoided in these patients because there is risk of cardiac temponade.

SHOULDER-HAND SYNDROME

It consists of pain and immobility of the left arm in the weeks and months following an acute myocardial infarction.

Prevention: Early mobilization reduces the incidence of this system.

Management: Physiotherapy.

POST-MYOCARDIAL INFARCTION SYNDROME (DRESSLER'S SYNDROME)

This is syndrome occurs 1-8 weeks after MI in about 5% of patients and is caused by an autoimmune response to damaged cardiac tissue or pericardium.

Clinical features

- Fever, malaise
- Chest pain due to pericarditis, pericardial effusion.
- Pleurisy, pulmonary infiltrates due to pneumonitis.

- Arthralgias
- Leukocytosis
- Raised ESR
- Antimyocardial antibodies may be found

Management

- Aspirin 600-900 mg every 4-6 hours.
- Steroids and NSAIDs should be avoided within 4 weeks of MI because they impair infarct healing and increase the risk of cardiac rupture. Steroids may be given if there is recurrence later.

LEFT VENTRICULAR ANEURYSM

- This is a late complication of MI (beyond 4-8 weeks) especially after anterior wall MI.
- Complications of aneurysms are heart failure, ventricular arrhythmias or emboli; they rarely rupture
- There is palpable visible paradoxical systolic pulsation in anterior chest wall. On auscultation fourth heart sound is heard.
- ECG shows persistent ST segment elevation
- X-ray chest may show abnormal rounded bulge.
- Diagnosis is confirmed by 2D echocardiography.

Management: anticoagulation, ACE inhibitors and anti-arrhythmic drugs as necessary. Surgical removal of the aneurysm may be necessary if arrhythmias or embolic or hemodynamic complications occur.

CAUSES OF SUDDEN CARDIAC DEATH

Coronary

- Acute myocardial infarction
- Chronic ischemic heart disease
- Post CABG
- Post resuscitation for cardiac arrest
- Congenital anomaly of coronary arteries
- Coronary artery embolism
- Coronary arteritis

Non- coronary

- Hypertrophic cardiomyopathy
- Dilated cardiomyopathy
- Right ventricular cardiomyopathy
- Congenital prolonged QT syndrome
- Brugada's syndrome
- Aortic stenosis, mitral valve prolapse
- Tetralogy of Fallot, transposition of great vessels
- VSD, PDA

RHEUMATIC FEVER (RF)

Rheumatic fever is an acute, inflammatory disease principally of children but also of adults that usually follows a pharyngeal infection with group A beta-hemolytic streptococci after a latent period of approximately 3 weeks. However pharyngitis may be so mild that history of sore throat is not available in 30-35% of cases. It does not follow streptococcal skin infection (impetigo).

Most likely it is the result of cross-reaction between the body immune response to streptococcal antigens & tissue antigens, principally in the heart.

Although only a small proportion of individuals with untreated streptococcal pharyngitis may develop rheumatic fever (3%), the incidence of the disease after streptococcal pharyngitis in patients who have had a previous episode of rheumatic fever is substantially greater (50%).

RF most commonly occurs between the ages 5 and 15 years, with peak about the age of 8 years. It is rare before age 4 and occasional cases are seen after the age 30.

Organs involved:
Connective tissues of heart, joints, skin, blood vessels and lungs.

INCIDENCE

Although no data is available regarding incidence in Pakistan, however incidence in developing countries is 100 per 100,000. Improved economic standards, better housing condition, decreased crowding in homes and schools and use of antibiotics and proper treatment of pharyngitis markedly declined rheumatic fever in advanced countries.

PATHOLOGY

The acute phase of rheumatic fever is characterized by exudative and proliferative inflammatory reactions involving connective or collagen tissue. Heart, joints, brain, skin and subcutaneous tissues are primarily affected.

In rheumatic carditis principally affected part is heart valve especially the aortic and mitral valves.

The characteristic lesion of rheumatic carditis is the Aschoff nodule, which is a granulomatous lesion with a central necrotic area.. The valve cusps become thickened by edema and by the infiltration of capillaries. Later a row of tiny vegetations is formed along the lines of closure of the valve leaflets.
Mitral valve is attacked in 75-80%, aortic valve in 30%, tricuspid and pulmonary valves in 5% of cases. Initial inflammation leads to valvular regurgitation (usually mitral, sometimes both mitral and aortic. Isolated aortic regurgitation is rare).
Carditis is noted in at least 50% of patients with acute rheumatic fever. There may be involvement of endocardium, myocardium or pericardium resulting in valvulitis, myocarditis or pericarditis. Myocarditis is suggested by tachycardia and heart enlargement. Severe valvular regurgitation or myocarditis may lead to cardiac failure.

In acute phase, dilatation of the mitral annulus may also result in mitral regurgitation. Chronic heart disease is a sequel to acute rheumatic carditis, and many of its features are the result of fibrosis of the heart valves during the healing of acute lesion.

Patient with acute rheumatic fever usually presents with relapsing fever, anorexia, fatigue, malaise and joint pain (arthralgia). Joint pain due to polyarthritis occurs early. Carditis may occur concomitant with polyarthritis or later after several weeks and presents with murmurs of regurgitation (usually mitral, sometimes both mitral and aortic regurgitation). There may be cardiac failure as a result of valvular regurgitation or myocarditis. Chest pain may occur due to pericarditis. In children chorea and subcutaneous nodules may also develop.
Rheumatic fever is a common long case in viva, it must be differentiated from endocarditis superimposed on chronic rheumatic heart disease.
Other disorders presenting with fever and joint pain are included in differential diagnosis are as follow:

- Lyme disease
- Brucellosis
- Miliary tuberculosis
- Cat scratch disease
- Staphylococcal arthritis
- Gonococcal or meningococcal arthritis
- Rheumatoid arthritis
- SLE
- Serum sickness

CLINICAL FEATURES

Acute rheumatic fever presents with sudden onset of fever, joint pain, malaise and loss of appetite. Epistaxis and abdominal pain may also occur. Since no single laboratory test, sign or symptom is specific to acute rheumatic fever Duckett-Jones criteria is used to help in diagnosis. These criteria are used for the initial episodes of RF not for the recurrence.
If supported by evidence of preceding group A streptococcal infection, the presence of two major criteria OR one major plus two minor criteria indicates a high probability of acute rheumatic fever.

REVISED DUCKETT-JONES CRITERIA

Major criteria

- Carditis
- Polyarthritis
- Chorea
- Erythema marginatum
- Subcutaneous nodules

Minor criteria

- Fever
- Arthralgia
- Previous rheumatic fever
- Raised ESR/ C- reactive protein
- Leukocytosis
- Prolonged PR interval on ECG

Supporting evidence of preceding streptococcal infection such as raised ASO titer or positive throat culture is necessary for diagnosis.

Carditis

About 40-60% patients with rheumatic fever have evidence of carditis. Carditis is most likely to be evident in children and adolescent. Any of the following features suggests the presence of carditis.

- Sinus tachycardia.
- Murmur of mitral and aortic regurgitation.
- Pericardial friction rub --- but it does not lead to constrictive pericarditis.
- Carey – Coombs murmur: mitral mid- diastolic murmur due to inflammation of mitral valve.

- Congestive heart failure, S3 gallop
- Mitral or aortic valve regurgitation murmurs.
- Cardiomegaly detected by physical signs, x-ray and echocardiography.
- Prolongation of PR interval (in 30-35% of cases). Second or third degree heart block may occur.
- ECG changes of pericarditis (raised ST segment) or myocarditis (inverted or flattened T wave).

Migratory polyarthritis

- Migratory polyarthritis is present in as many as 75% of cases, most often affecting large joints such as knees, elbows, ankles and wrists.
- The joints are swollen, red and tender. As the inflammation in one joint decreases, another becomes affected (migratory arthritis). The arthritis of rheumatic fever is extremely painful and lasts for 2-3 weeks and subsides without residual deformity.
- Prompt response to therapeutic dosage of salisylates (aspirin) within 24 hours is characteristics. If joint pain persists after 24 hours of starting aspirin, diagnosis of acute rheumatic fever should be re- evaluated.

Sydenham's chorea

Sydenham's chorea develops in less than 10% of cases, however it is the most diagnostic feature of rheumatic fever if present. It can develop several months after streptococcal infection. Chorea is characterized by involuntary choreoathetoid movements primarily of the face, tongue, and upper extremities. Girls are more frequently affected and occurrence in adults is rare.

Erythema marginatum and subcutaneous nodules

These are rare major manifestations occurring in less than 10% of cases.

- Erythema marginatum: Pink rash with slightly raised edges found mostly on the trunk and limbs
- Subcutaneous nodules: Painless, pea-sized hard nodules beneath the skin, may also occur over tendons, joints and bony prominences.

COMPLICATIONS

- Congestive heart failure
- Rheumatic heart disease
- Arrhythmias
- Pericarditis
- Pericardial effusion
- Rheumatic pneumonitis

INVESTIGATIONS

Although the diagnosis of rheumatic fever is clinical, following investigations may be helpful:

Throat swab culture

Throat swab culture for group A streptococcus.

Antistreptolysin O titer (ASOT):

The rising titer of antibodies against streptococci (ASOT) indicates a recent streptococcal infection. ASOT is elevated in about 80% of cases. If ASOT is normal, it should be rechecked after a week, as it may then be elevated. If not elevated then anti-DNase B is performed. Both types of titers are elevated for weeks or months.

ESR and C-reactive protein:

- ESR and C-reactive protein are the acute phase reactants indicating tissue inflammation and are elevated during the acute stages of the disease.
- Erythrocyte sedimentation rate (ESR) is useful in monitoring the course of the disease; it usually returns to normal as the rheumatic activity subsides. ESR may be elevated in patients with anemia and may be suppressed to normal levels in patients with congestive heart failure. Unlike the ESR, the CRP level is unaffected by anemia or cardiac failure.

Blood CP

- Leukocytosis with TLC 12000-15000/mm^3 may be observed in acute stage of RF.
- Anemia is usually mild to moderate and is normocytic normochromic in morphology.

Chest x-ray: may be normal or indicates cardiomegaly, pulmonary edema and increased pulmonary vascularity.

ECG: may indicate prolonged PR interval, heart block, features of pericarditis and myocarditis.

Echocardiography: It may show mitral regurgitation due to prolapse of anterior mitral leaflet, heart dilatation and valve abnormality. Myocardial dysfunction and pericardial effusion may also be seen.

> **INVESTIGATIONS IN ACUTE RHEUMATIC FEVER**
>
> **Evidence of a systemic Illness**
> Fever, leukocytosis and raised ESR are usual, non-specific but useful for following the progress of the disease once diagnosed.
>
> **Evidence of preceding streptococcal infection**
> Throat swab culture: Culture of group a beta-hemolytic streptococcal from a throat swab is positive only in a minority by the time rheumatic fever is clinically manifest. Positive cultures can sometimes be obtained from family members and contacts.
>
> Antistreptolysin O antibodies (ASO titer): useful evidence of recent streptococcal infection, especially if a rising titer can be shown. In the absence of rising titer, a level of > 200 units in adults or > 300 units in children is also usually evidence of recent infection.
>
> **Evidence of carditis**
> The chest radiograph may show cardiac enlargement or pulmonary congestion ECG changes include first and second degree heart block, features of pericarditis, T wave inversion and reduction in QRS voltages. Echocardiography is useful for showing cardiac dilatation and valve abnormalities.

TREATMENT

Complete bed rest

Patient should be kept at strict bed rest until:

- The temperature returns to normal
- ESR returns to normal.
- Resting pulse rate is normal (< 100/min in adults).
- ECG returns to baseline.

Salicylates

- Salicylate (Aspirin) markedly reduces fever and relieves joint pain and swelling. It is given as 100mg/kg/day in 4-5 divided doses. Tinnitus, nausea, vomiting and anorexia are common dose-related toxicities associated with salicylism. After the polyarthritis has been controlled successfully for 2 weeks, the aspirin dosage should be tapered for an additional 6 weeks. Aspirin if stopped abruptly can lead to rebound of symptoms.

Duration of secondary prevention in patients with rheumatic fever (RF)	
RF with carditis and residual valvular disease	Life-long prophylaxis
RF with carditis but no residual valvular disease	10 years or well into adulthood whichever is longer
RF without carditis	5 years after the last attack or age 21 whichever is longer.

Corticosteroids

A short course of corticosteroids (prednisolone 40-80 mg/d) for 2 weeks, after which the dosage is tapered slowly over 3 weeks usually causes rapid improvement and is indicated when response to salicylate has been inadequate or there is severe arthritis or carditis accompanied by congestive cardiac failure.

However it must be noted that aspirin and corticosteroid promptly relieve symptoms but they have no effect on the coarse of carditis or diminishing incidence of residual heart disease.

PREVENTION

Primary prevention

Prevention of primary attacks of rheumatic fever depends on prompt recognition and proper treatment of group A streptococcus tonsillopharyngitis.

Penicillin

Intramuscular benzathine penicillin (single injection) is the antimicrobial agent of choice, penicillin may be given orally (penicillin V) but the duration of treatment is 10 days.

- Benzathine penicillin (Penidure LA) intragluteally for the eradication of infection.
  - 1.2 million units above weight 27 kg.
  - 0.6 million units below weight 27 kg.

Macrolides

Erythromycin 250 mg 6 hourly for 10 days can be used in penicillin allergic patient.

Azithromycin may be given for 5 days. First day 500mg single dose then 250 mg as a single dose for 4 days.

Cephalosporin
A 10 -day course of an oral cephalosporin such as cephalexin (Ceporex) may be given as an alternative in penicillin allergic patient.

Secondary prevention

Secondary prevention means prevention from recurrence of rheumatic fever that requires continuous antimicrobial prophylaxis.

Penicillin
Benzathine penicillin (Penidure LA) 1.2 million units (if weight >27kg) IM every 4 weeks (every 3 weeks where incidence of RF is high such as in Pakistan).

Sulfonamide or erythromycin
If patient is allergic to penicillin, sulfadiazine 1g daily or erythromycin 250 mg orally twice daily may be substituted.

PROGNOSIS

- Initial episodes of rheumatic fever may last months in children and weeks in adults.
- The immediate mortality rate is 1-2%.
- Persistent rheumatic carditis with cardiomegaly, heart failure, and pericarditis imply a poor prognosis.
- After 10 years, two-thirds of patients will have detectable valve disease but symptomatic valvular disease or persistent cardiomyopathy occurs in less than 10% of cases. Mitral valve is involved in 90% of cases; next affected valve is aortic valve.

CHRONIC RHEUMATIC HEART DISEASE

Chronic rheumatic heart disease results from single or repeated attacks of rheumatic fever that produce rigidity and deformity of valve cusps, fusion of the commisures, or shortening and fusion of chordae tendinae. Stenosis or regurgitation

INFECTIVE ENDOCARDITIS

Microbial infection of a heart valves or lining of a cardiac chamber is called infective endocarditis.

PREDISPOSING FACTORS

- Rheumatic heart diseases: in order of sequence mitral regurgitation, mitral stenosis, aortic stenosis, aortic regurgitation.
- Congenital heart diseases: such as bicuspid aortic valve, mitral valve prolapse, calcified aortic valve disease, hypertrophic subaortic stenosis, VSD, coarctation of aorta or patent ductus arteriosus.
- Prosthetic valves.

MICROBIOLOGY OF NATIVE VALVE ENDOCARDTIS

Bacteria

Streptococci	
Viridans	30 – 40 %
Enterococci	10 – 15 %
Other streptococci	20 – 25 %
Staphylococci	
Aureus	9 – 27 %
Coagulase negative	1 – 3 %
Gram negative bacilli	Total 3 – 8 %
Hemophilus	
Anaerobes	
Other organisms	Less than 2%
Rickettsia, fungi	

MICROBIOLOGY OF PROSTHETIC VALVE ENDOCARDTIS

Within 2 months of valve implantation

- Coagulase negative staphylococcus (staph. epidermidis) 33%
- Staphylococcus aureus 22%
- Gram – negative bacilli 13%
- Fungi – Candida 8%

After 12 months
(Similar to native valve endocarditis)

- *Streptococcus viridans* are commensals in the upper respiratory tract and a common cause of periodontal infections. They may enter the blood stream on chewing, teeth brushing, or dental extraction.
- *Enterococcus fecalis* is found in perianal and fecal bacterial flora. Infection with this organism is more common in older men with prostatic disease, in women with genitourinary infections.
- *Streptococcus bovis* is associated with large bowel carcinoma.
- *Staphylococcus aureus* is a common cause of acute endocarditis and originates from skin infections, abscesses or intravenous lines including IV drug abuse.
- *Post-operative endocarditis* follows cardiac surgery and affects native or prosthetic valve. The most common organism is staphylococcus albus.
- *Gram-negative bacilli* are mostly associated with prosthetic valves.
- *Fungal infections* (Candida, Aspergillus) may attack previously normal or prosthetic valves, usually affects drug addicts and immunosuppressed patients.

NONBACTERIAL THROMBOTIC ENDOCARDITIS
Noninfective causes of endocarditis are:

- Old age
- Malignancy
- Disseminated intravascular coagulation
- Uremia
- Burns
- SLE

PATHOLOGY

Infection occurs along the edges of the heart valves. This is more common on the left side producing mitral and aortic regurgitation. Right sided valves (usually tricuspid are involved in IV drug abusers.

The endothelial damage by infection leads to deposition of platelets and fibrin, which are colonized by blood-borne organism. This mass that is composed of fibrin, platelets and infecting organisms is known as vegetation. The vegetations may become large enough to cause obstruction or break away as emboli. Therefore following basic pathological features may be seen:

Local destructive effects of intracardiac infection:

- Destruction of the valve cusp, producing ulceration and ultimately regurgitation.
- Rupture of chordae tendineae.
- Paravalvular abscess leading to destruction of conduction system (causing arrhythmias) and purulent pericarditis.
- Large vegetations may cause functional valvular

Embolism
Embolization fragments of vegetations producing splenic, renal, myocardial or pulmonary infarctions.

Metastatic infection
Septic emboli may cause infection in any organ or tissue producing abscess there.

Deposition of immune complexes
Deposition of immune complexes (antigen antibody complexes) in various tissues producing extracardiac manifestations e.g. arthralgia, Roth spots, Janeway lesions, focal glomerulonephritis and acute vasculitis.

TYPES
Clinically and pathologically endocarditis may be divided into three types

1. Subacute endocarditis
2. Acute endocarditis
3. Prosthetic endocarditis

Note: Endocarditis is now divided according to the causative organism and the valve involved. This distribution of acute and subacute endocarditis is less commonly used now because subacute endocarditis may abruptly develop life-threatening complications and is not always subacute.

Subacute endocarditis
It results from an organism of relatively low virulence affecting mostly rheumatic or congenitally abnormal valve. The commonest organism is streptococcus viridans. This should be suspected when a patient known to have congenital or valvular heart disease develops a persistent fever, unusual tiredness, night sweats, weights loss or develops new signs of valve dysfunction or heart failure.

Acute endocarditis
This is usually due to a highly virulent and invasive organism e.g. staphylococcus aureus. It can affect damaged valves but can also occur in hearts with no previous defects such as in intravenous drug abuse. Vegetations may be very large and valve destruction is greater than subacute endocarditis. Patient usually presents with severe febrile illness with prominent and changing heart murmurs. Clinical stigmata of chronic endocarditis are usually absent.

Prosthetic endocarditis
This is endocarditis following cardiac surgery in which prosthetic heart valves are used. Common organism is staphylococcus (S. epidermidis and S. aureus). This produces myocardial abscesses and damage to the conduction system.

CLINICAL FEATURES

Features of bacteremia

Fever
Fever that has lasted several days to 2 weeks in a patient having congenital or valvular heart disease should be considered for endocarditis. Fever may be absent in older individuals, patients with CCF and CRF.

Petechiae
Small petechial or mucosal hemorrhages occur due to vasculitis. They are small, and red, usually with pale center, appearing mostly in mucosa of pharynx and conjunctiva. Roth sots are petechial hemorrhages occurring in retina.

Splenomegaly
Splenomegaly develops in 30-40% of cases in long standing endocarditis only.

Features of immune complexes
Antibodies and bacterial antigens combine to form circulating immune complexes. Deposition of these immune complexes produces the following features:

Janeway lesions:
They are small, flat, erythematous, non-tender macules on thenar and hypothenar eminence.

Splinter hemorrhages
They develop under the finger or toe nails.

Osler's nodes:
They are hard, painful, tender subcutaneous swellings occurring at the fingertips, toes, palms and soles. They may be the result of vasculitis or embolism.

Features of valvular dysfunction

Murmurs

Vegetations which hinder the flow of blood produce turbulence and therefore produces abnormal heart sounds (murmurs). With changes in the size of vegetations the character of the murmurs changes, a feature that is typical of infective endocarditis.

Regurgitation

Progressive destruction of valve may produce valve perforation and regurgitation.

Features of embolism

Emboli from the friable vegetations are common producing the following features:

Infarctions

With left-sided endocarditis, systemic embolism causes multifocal areas of infarction in the following organs:

- Brain:- resulting in embolic stroke (more frequent with S. aureus)
- Kidney:- presenting as hematuria.
- Heart:- causing myocardial infarction
- Intestine:- causing intestinal infarction.
- Spleen:- causing splenic infarction.
- Extremities:- causing gangrene.

Right-sided endocarditis causes pulmonary embolism.

PRESENTATIONS OF INFECTIVE ENDOCARDITIS

1. **Features of infection**: Fever, night sweats, weight loss, fatigue, myalgia, arthralgia.
2. **Features of embolism:** patient may present directly with embolic features such as stroke, severe limb pain, pulmonary or myocardial infarction .
3. **Cardiac features:** signs and symptoms of underlying heart disease, new or changing murmur, cardiac failure due to valvular destruction.
4. **Features of immune vasculitis:** splinter hemorrhage, clubbing, petechial hemorrhage, Janeway lesion, Osler's nodes

EXAMINATION OF PATIENT WITH ENDOCARDITIS

- **Hands**: Clubbing, splinter hemorrhage, Osler's nodes and Janeway lesions.
- **Eyes**: Roth's spots in fundus, conjunctival petechiae.
- **Mouth:** check temperature with thermometer
- **Precordium**: Murmurs of congenital or valvular heart disease, signs of cardiac failure, scar of previous cardiac surgery.
- **Lungs**: crepitations due to failure
- **Abdomen:** splenomegaly.
- **Lower limb**: Neurological signs for embolic disease e.g. weakness or paralysis.
- **Urine analysis** for hematuria and proteinuria.
- Look for source of infection.

CLINICAL FEATURES OF INFECTIVE ENDOCARDITIS

General systems	Approximate %
Malaise	95
Clubbing	10
Cardiac	
Murmurs	90
Cardiac failure	50
Arthralgia	25
Pyrexia	90
Skin lesions	
Osler's nodes	15
Splinter hemorrhage	10
Janeway lesions	5
Petechiae	50
Eyes	
Roth spots	5
Conjunctival	Rare
Splinter hemorrhages	
Splenomegaly	40
Neurological	
Cerebral emboli	20
Mycotic aneurysm	10
Renal	
Haematuria	70

INVESTIGATIONS

1. Blood culture

- Blood culture is the crucial investigation
- Three sets of blood culture should be taken from different venepuncture sites over 24 hours before starting antibiotics. Each set should include two flasks one for aerobic and other for anaerobic culture, into each of which at least 10ml of blood should be placed.
- Blood culture is positive in about 95% of cases and negative in 5% cases.

Causes of negative culture

- Negative cultures in 5% of patients are because of antibiotic therapy before obtaining culture (by general practitioner or patients themselves).
- Fungal infection
- Organisms that require special media e.g. legionella.
- Slow growing organisms e.g. brucella, anaerobes.

Solution of the problem

If antibiotics are given prior to culture and patient is stable, then withhold further antibiotics for 2-3 days so that appropriate cultures can be obtained.

2 Other blood tests

- Anemia – normocytic normochromic
- C-reative protein and ESR are raised
- WBC count is elevated in acute endocarditis while usually normal in subacute endocarditis.
- Thrombocytoenia – may be present but rare.

3. Echocardiography

It is key investigation for detection of

- Vegetations
- Valve damage
- Abscess formation

The sensitivity of transthoracic echocardiography for detection of vegetations is approximately 65%; therefore, infective endocarditis cannot be reliably ruled out if transthoracic echocardiography is negative.

The sensitivity of trans-esophageal echocardiography (TEE) is 85-95% for detection of vegetations and is particularly useful for identify valve ring abscesses.

Transthoracic echocardiography can detect vegetations of 3-5 mm while the transesohageal echocardiography can detect smaller vegetations of 1 – 1.5 mm.

4. ECG

This may show myocardial infarction or conduction defects (due to abscess formation).

5. Chest x-ray

This may indicate cardiac failure or pulmonary embolism in right – sided failure.

6. Urine analysis

Proteinuria may occur and microscopic hematuria is always present.

7. Serological tests

Tests for immune complexes such as low C3 and C4 complements. RA factor is positive in 50% of cases and ANA in 20% of cases.

INVESTIGATIONS IN ENDOCARDITIS

- Blood culture
- Echocardiography
- Blood CP/ESR
- Urine analysis
- ECG
- X-ray chest

DIAGNOSIS OF ENDOCARDITIS

The diagnosis of endocarditis must be suspected and investigated when patient with fever presents with one or more of the cardinal elements of infective endocarditis as following:

- Predisposing cardiac lesion.
- Bacteremia
- Embolic phenomenon
- Active endocardial process

The modified Duke's criteria provide a scheme that facilitates evaluating patients for endocarditis.

MODIFIED DUKE'S CRITERIA FOR THE DIAGNOSIS OF ENDOCARDITIS

MAJOR CRITERIA

1. **A positive blood culture**
   - A. Positive blood culture for a *microorganism* that typically causes infective endocarditis (Organisms are streptococcus viridans, streptococcus bovis, HACEK group or community acquired staphylococcus or enterococci in the absence of primary focus).
   - *B. Persistently positive cultures*
     - From two separate blood cultures drawn more than 12 hours apart OR
     - All of three or a majority of four or more cultures with first and last drawn at least one hour apart.
2. **Evidence of endocardial involvement.**
   - *A. Positive echocardiography*
     - Definite vegetation on valve or supportive structures OR
     - Myocardial abscess OR
     - New partial dehiscence of prosthetic valve
   - *B.* Development of *new murmur of regurgitation.*

Minor criteria

1. The presence of predisposing factor.
2. Fever > 38°C (100.4 °F)
3. *Vascular phenomena*
   - Major arterial emboli
   - Septic pulmonary infarcts
   - Mycotic aneurysm
   - itracranial hemorrhage
   - conjunctival hemorrhage
   - Janeway lesion
4. *Immunologic phenomenon* such as glomerulonephritis, Osler's nodes, Roth spots.
5. *Microbiologic evidence*
   - Positive blood culture but not meeting the major criteria. OR
   - Serological evidence of active infection with organism consistent with infective endocarditis
6. *Echocardiogram* consistent with infective endocarditis but not meeting the major criteria.

Definite endocarditis: A definitive diagnosis may be made with if two major criteria, or one major and three minor, or five minor criteria are fulfilled.
Possible endocarditis: finding of one major plus one minor or three minor criteria indicates possible endocarditis; it should be treated as definite endocarditis.

If none of the criteria are met or if the patient becomes afebrile within 4 days of starting antibiotics, endocarditis is unlikely.

SUMMARY OF DUKE'S CRITERIA

Major criteria
1. Positive blood culture
2. Echo consistent of endocarditis or clinically new murmur of regurgitation.

Minor criteria
1. Predisposing factors
2. Fever
3. Vascular phenomena
4. Immunological phenomina
5. Microbiological evidence of infection with organism consistent with infective endocarditis
6. Positive echo for infective endocarditis but not as in major criteria.

COMPLICATIONS

Cardiac complications
- Congestive heart failure
- Valvular damage leads to valvular regurgitation
- Valvular stenosis
- Abscess extending to myocardium causing conduction disturbances, extending to pericardium causing purulent pericarditis.
- Coronary embolism
- Prosthetic dehiscence

Extracardiac complications
- Systemic embolism (causing stroke, renal infarct, splenic infarct or ischemic limb).
- Infected emboli can cause abscesses elsewhere in the body.
- Right-sided infected emboli may cause pulmonary abscess or infarction.
- Mycotic aneurysm
- Immune complex deposition causing glomerulonephritis.

ANTIMICROBIAL THERAPY FOR ENDOCARDITIS

Organism	Drug of first choice	Dose & duration	Alternatives	Dosage & duration
Strep. Viridans	Benzylpenillin i.v. + Gentamicin i.v.	2-3 million units 4 hourly 80 mg 12-hourly ***Duration 2-weeks***	Cefriaxone or Vancomycin	2g once daily i.v. 15mg /kg 12-hourly Duration 4-weeks
Strep. fecalis (enterococcus)	Amoxycillin or ampicillin i.v. + gentamicin i.v.	2g 4-hourly 80 mg 12-hourly ***Duration 4 weeks***	Cefriaxone or Vanomycin	2g once daily i.v. 1.5mg/kg 12-hourly Duration 4-weeks
Staphylococcus Penicillin sensitive	Benzyl penicillin + gentamicin	2-3 million units 4 hourly *for 4 weeks* 80-120mg 12-hourly *for 1 week*		
Penicillin resistant methicilin sensitive	Cloxacillin + gentamicin	2g 4-hourly for *4 weeks* 80-120mg 8 hourly *for 1 week*		
Penicillin and methicillin resistant	Vanomycin + gentamicin	1g 12-hourly for 4 weeks 80-120mg 8-hourly for 1 week.		

INDICATIONS FOR CARDIAC SURGERY (VALVE REPLACEMENT) IN INFECTIVE ENDOCARDITIS

- Acute heart failure due to valvular regurgitation that does not resolve promptly with medical therapy needs immediate surgery and valve replacement.
- Failure of antibiotic therapy after 7-10 days. (persistent fever and persistently positive blood culture despite antimicrobial therapy).
- Fungal infection (surgery always required)
- Gram- negative bacilli infection (surgery usually required).
- Large vegetations on left sided heart valves with evidence of, or 'high risk of, systemic emboli.
- To drain myocardial abscesses.
- Recurrent infection with the same organism especially infected prosthetic valves.
- Paravalvular infection causing conduction disturbances, or a paravalvular abscess or fistula.
- Aortic valve endocarditis who develop first or second degree AV block

ANTIBIOTIC PROPHYLAXIS AGAINST ENDOCARDITIS

Procedure	Antibiotic
Local anesthesia	
Dental or upper respiratory tract procedures	Amoxycillin orally 3g 1 hr before
If allergic to or received penicillin in last month	Clindamycin orally 600 mg 1 hr before
General anesthesia	
Dental or upper respiratory tract procedures	Amoxycillin 1 g i.v. at induction followed by 0.5 g 6-hours later orally
If allergic to penicillin	Vancomycin 1g IV infusion over 1hr before induction plus gentamycin 120mg IV
Genitourinary procedures	Amoxycillin 1g IV plus gentamicin 120mg IV plus amoxycillin 0.5g 6-hrs later
If allergic to penicillin	Vancomycin 1g IV over 1 hr plus gentamicin 120mg IV

EXAMINATION OF CARDIOVASCULAR SYSTEM

SCHEME OF CARDIOVASCULAR SYSTEM EXAMINATION

Position the patient at 45 degree and make sure the chest and neck are fully exposed in males while in females modesty should be adapted and exposure is required if necessary.

1. General appearance of patient such as anxiety, breathlessness, generalized wasting and pain.
2. Shake hands and assess the peripheral circulation (cold or warm) sweating, clubbing, splinter hemorrhage.
3. Always palpate radial pulses on both sides and measure rate and rhythm (in Takayasu arteritis radial pulse may be absent on other side and this may be the short case in viva).
4. Palpate brachial pulses of both sides and measure blood pressure.
5. Examine face; look for anemia, cyanosis and features of hypercholesterolemia.
6. Examine and measure jugular venous pulse (JVP).
7. Palpate carotid pulses; one by one, assess quality and listen for bruit (very important in stroke patient).
8. Look for thyroid enlargement.
9. Examine precordium: inspection, palpation and auscultation.
10. Auscultate back of chest for crepitations and examine for sacral edema.
11. Examine abdomen for hepatomegaly and ascites.
12. Assess femoral pulses and feel for radiofemoral delay.
13. Examine legs: palpate pulses, look for edema.
14. Examine the optic fundi.

SCHEME OF CARDIOVASCULAR SYSTEM EXAMINATION IN VIVA SHORT CASE

Complete CVS examination is very lengthy and is not asked in one short case, usually patient has valvular or congenital heart disease and command is to examine precordium; therefore start from precordium inspection, palpation and auscultation, then auscultate lung bases and then perform general physical examination related to CVS such as pulse, clubbing, anemia, cyanosis, thyroid, JVP, carotid, hepatosplenomegaly, radiofemoral delay, sacral and pedal edema and describe the examination in the same sequence. Examination is incomplete if you do not perform general physical examination related to that particular system. There is no need to get permission for it, this is understood and you must perform it. You will get valuable information from general physical examination that is very helpful to reach the diagnosis.

EXAMINATION OF PULSE

- Apply three fingers over the radial pulse at the right wrist while the patient's hand is slightly flexed and pronated. Count the pulse for 15 seconds and multiply by four to obtain pulse rate in beats per minute. Normal pulse is 60-100 beats per minute.
- Rate and rhythm are appreciated in radial pulse while volume and most of the characters are felt on proximal pulses such as brachial, carotid and femoral.
- Other pulses such as brachial, carotid, femoral, popliteal, dorsalis pedis and posterior tibial are also examined and *compared* from opposite side.

CAUSES OF BRADYCARDIA

Bradycardia: pulse rate < 60 beats per minute.

Regular rhythm:

- Drugs e.g. beta-blocker, digoxin, calcium channel blocker.
- Hypothyroidism
- Raised intracranial pressure
- Obstructive jaundice
- Third or second degree heart block
- Myocardial infarction.

Regularly irregular rhythm

- Sinus arrhythmia (normal slowing of the pulse with expiration). This is a normal phenomenon that is lost in heart failure and autonomic neuropathy.
- Second degree heart block.

Irregularly irregular rhythm

- Atrial fibrillation

RELATIVE BRADYCARDIA

Normally pulse rises 10 beats per min for each degree ^{0}F rise in body temperature. If pulse rate is slower than expected for the body temperature, it is called relative bradycardia. Causes are typhoid fever and viral fever.

CAUSE OF TACHYCARDIA

Tachycardia: pulse rate> 100 beats per minute.

Regular rhythm

- Hyperdynamic circulation due to:
  - Exercise, emotion (e.g. anxiety)
  - Fever: 10 beats /min increase per degree °F
  - Pregnancy
  - Thyrotoxicosis
  - Anemia
  - Beri beri
- Congestive cardiac failure
- Drugs e.g. salbutamol
- Hypovolemia
- Supraventricular tachycardia
- Ventricular tachycardia

Irregular rhythm

Atrial fibrillation

RHYTHM OF PULSE

Regular pulse

Regular pulse rhythm means that all pulses are occurring at regular interval and equal in volume.

Irregular pulse

When the pulse is irregular. It is important to identify nature of the irregularity as following:

- *Regularly irregular*
  It means irregularity occurs after regular interval. It occurs in digitalis toxicity and Mobitz type – 1 heart block.
- *Irregularly irregular*
  It means pulse is completely irregular in rate and volume. It occurs in atrial fibrillation and multiple ventricular ectopics.

PULSE VOLUME

High volume pulse

It results from aortic regurgitation or vasodilation.

- *Physiological causes of vasodilation*
  Exercise, emotion, heat and pregnancy.
- *Pathological causes of vasodilation:*
  Fever, thyrotoxicosis, anemia, Paget's disease of bone, and drug therapy.

Low volume pulse

It results from reduced stroke volume due to cardiac failure or peripheral vascular disease.

CHARACTER OF PULSE

Character of pulse is best appreciated in large arteries such as brachial, carotid or femoral, but collapsing pulse and pulsus alternans may be better felt in radial artery. Character of pulse is very important in clinical diagnosis of valvular heart disease and is very commonly asked in examination.

Collapsing or Water hammer pulse

Collapsing pulse is a rapidly rising pulse which collapses suddenly as arterial pressure falls rapidly during late systole and diastole. Most common cause is chronic aortic regurgitation. It is checked by elevating the patient's arm. It is also called bounding pulse. Higher the pulse pressure more characteristic will be the pulse.

Pulsus plateau

It is a slow volume pulse that rises slowly occurring aortic stenosis. It is also called anacrotic pulse. It is best felt in carotid artery.

Pulses alternanas

It is a regular pulse with alternating weak and strong pulse occurring in severe left ventricular failure and dilated cardiomyopathy.

Pulsus paradoxus

It is a pulse that increases in volume on expiration and decreases in volume on inspiration. Although it is a normal phenomenon, yet not detectable in normal individual. When the phenomenon is exaggerated, it is called pulses paradoxus.

Pulsus paradoxus can be confirmed by checking blood pressure that rises more than 10 mmHg during normal expiration and falls during inspiration. While taking blood pressure, cuff is deflated gradually, note the level at which Krotokoff sounds appear, this is heard during expiration phase and disappear during inspiration. Now continue deflating and look for both respiratory phases and note the level at which sounds are audible during both phases. In pulsus paradoxus difference between these two levels is more than 10 mmHg.

* Pulsus paradoxus occurs in cardiac temponade, constrictive pericarditis and acute severe bronchial asthma (status asthmaticus).

Pulsus bisferiens

It is a double peaked pulse in which two systolic peaks are palpable in one pulse. It occurs in combined aortic stenosis and regurgitation. It is best felt in the carotid.

Pulsus deficit

In this type of pulse, there is a deficit between the heart rate and the peripheral pulse. Heart rate is more than the peripheral pulse and is seen in atrial fibrillation. Compare heart rate and peripheral pulse simultaneously by auscultating the heart and feeling the pulse at the same time, heart rate is always more than the pulse rate. *In patient of atrial fibrillation actual pulse rate is that counted through auscultation.*

Pulsus bigeminus

In this type of pulse a strong and a week pulse occur close to each other followed by a pause therefore two pulses occur in pair. Pulsus bigeminus occurs in digitalis toxicity and with regularly alternating ectopic beats. It is palpated in radial artery. ECG confirms the diagnosis.

COMPARISON OF PULSES

Pulses of both sides are palpable simultaneously except carotid and compare for volume. Radiofemoral delay occurs in coarctation of aorta and volume of radial pulses is unequal in Takayasu's arteritis and Subclavian steel syndrome.

CONDITION OF THE VESSEL WALL

Vessel wall is palpated by occluding the brachial artery with the thumb of one hand and the radial artery is felt by rolling movements of the vessel by three fingers. Thickened vessels due to arteriosclerosis in elderly are palpable.

MEASUREMENT OF BLOOD PRESSURE

- Blood pressure is measured with sphygmomanometer. Systolic blood pressure is the peak pressure that occurs in the artery following ventricular systole and the diastolic blood pressure is the level to which the arterial blood pressure falls during ventricular diastole.
- Normal blood pressure is defined as a systolic pressure less than 140 and diastolic less than 90 mmHg.
- The usual blood pressure cuff width is 12.5 cm. This is suitable for a normal sized adult forearm. However in obese patients with large arm, normal sized cuff will overestimate the blood pressure and therefore a large cuff must be used.
- Cuff is wrapped around the upper arm, first take blood pressure with palpatory method then inflate again more than 10mmHg of systolic pressure measured by palpatory method and now measure BP by auscultatory method.

Hypertension

Blood pressure more than 140/90 is called hypertension.

Postural hypotension

Blood pressure should routinely be taken with the patient lying and standing (for 2min), a fall of more than 15 mmHg in systolic blood pressure or 10 mmHg in diastolic blood pressure on standing is abnormal and is called postural hypotension. It may lead to dizziness or syncope. It is a common complaint of cardiac patient especially elderly who is taking ACE inhibitors and diuretic for hypertension or heart failure.

Causes of postural hypotensation

- Hypovolemia e.g. dehydration, bleeding.
- Drugs: vasodilators, diuretics, tricyclic antidepressants.
- Addision's disease.
- Autonomic neuropathy; e.g. in diabetes mellitus, amyloidosis, Shy-Drager syndrome.
- Hypopituitarism.

JUGULAR VENOUS PULSATION (JVP)

Examination of internal jugular vein provides valuable information regarding the right atrial pressure and in this way information is obtained about right atrial and right ventricular function.

Position of the patient

The patient must lie down at 45 degree to the horizontal with his or head on pillows and in good light for clear exposure.

Method

- The internal jugular vein is medial to the sternomastoid muscle, external jugular vein is lateral to it but internal jugular is more reliable. Jugular vein pulsations reflect movements of the top of the column of blood which extends into the right atrium. This level of blood column indicates pressure changes in right atrium.
- Sternal angel is taken as zero point and the maximum height of pulsations in the internal jugular vein can be measured in centimeters by keeping a scale on sternal angle vertical to the ground and another scale horizontal to the ground at the level of upper limit of blood column.
- Sometimes carotid pulsation looks like JVP and it should be differentiated from it as following:

Differentiation between JVP and carotid pulsation

JVP	Carotid pulsation
It is visible but not palpable	It is palpable
There are usually two upstrokes. The best way is to palpate left carotid and look at right JVP; with one carotid pulsation there are two upstrokes of JVP	Only one upstroke
It decreases on inspiration	No effect with respiration.
It is at first obliterated and then filled from above when light pressure is applied at the base of the neck.	Can not be obliterated.
Hepatojugular reflex elevates the level of JVP	No effect

ASSESSMENT OF JVP

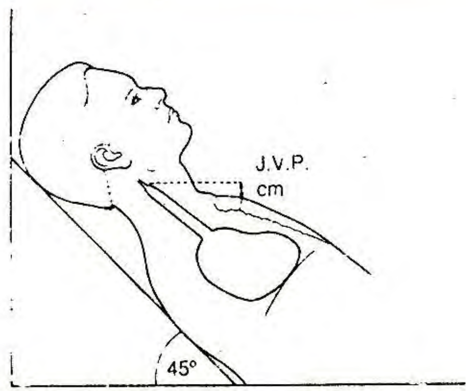
The jugular venous pressure (JVP) is assessed for height and character as following:

Height of JVP

- When the JVP is more than 3 cm above the zero point, it is said to be elevated and it indicates that right heart filling pressure is raised. This may be a sign of right ventricular failure or volume overload.
- Kussmaul's sign: normally JVP level falls with inspiration while in constrictive pericarditis or pericardial effusion it rises with inspiration, this is called Kussmaul's sign.

Causes of raised JVP

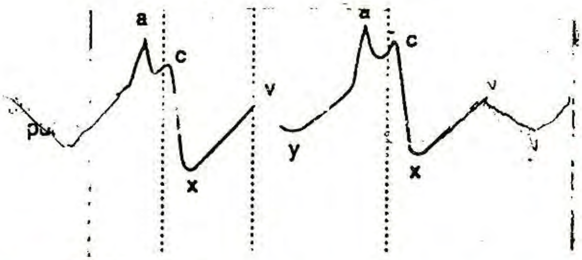
- Right ventricular failure
- Tricuspid stenosis or regurgitation
- Pericardial effusion or constrictive pericarditis
- Superior vena caval obstruction (JVP is elevated but not pulsatile).
- Fluid overload.



Character of JVP

There are two positive waves in the JVP 'a' and 'v' and two negative waves (descents) 'x' and 'y'.

- *The 'a' wave:* It results from right atrial contraction that causes rise in JVP.
- *The 'x' descent:* it results from atrial relaxation resulting in falling of pressure in atrial chamber.
- *The 'c' wave:* it is seen on 'x' descent and results from transmitted carotid pulsation.
- *The 'v' wave:* it is a positive wave that results from elevation of pressure in right atrium due to pooling of blood during atrial diastole.
- *The 'y' descent:* it is a negative wave due to emptying of blood from atrium into ventricle reducing the pressure of right atrium.



- a= atrial systole,
- c= transmitted pulsation of carotid artery at the onset of ventricular systole
- v= peak pressure in right atrium immediately prior to opening of tricuspid valve
- x = xdescent due to atrial relaxation
- y= y descent at commencement of ventricular filling

Abnormalities of JVP character

- Giant 'a' waves: They are large and occur when right atrial pressure is raised because of obstruction to outflow (e.g. tricusid stenosis).
- Cannon 'a' waves: In complete heart block the atria and ventricle contract asynchronously at their own rates. When they contract simultaneously i.e. right atrium contracts against closed tricuspid valve, a giant 'a' wave is produced. This occurs intermittently.
- Large 'v' wave: It results from reflux of blood into right atrium in tricuspid regurgitation.
- The 'x' descent is not present in atrial fibrillation.
- Slow 'y' descent is seen in tricuspid stenosis and atrial myxoma.
- Rapid or steep or prominent 'y' descent is seen in constrictive pericarditis.

EXAMINATION OF RPECORDIUM

INSPECTION

- Look for deformities such as kyphoscoliosis.
- Scar of previous surgery.
- Bulging of precordium due to cardiac hypertrophy.
- Pulsations.
- Apex beat normal or displaced.

PALPATION

Localization of apex best:

Palpate for the apex beat position and after localization count the correct number of interspaces. The normal position is in the 5^{th} intercostals space, medial to the midclavicular line.

- Cardiac cause of apex beat displacement is left ventricular dilatation.
- Respiratory causes may be large pleural effusion, pneumothorax, fibrosis and collapse of the lung.

Character of apex beat

- Normal character neither heaving nor tapping.
- <u>Tapping:</u> It is palpable first heart sound and is found in mitral stenosis.
- <u>Heaving:</u> It is a forceful apex beat that causes lifting the examiner's hand from the chest. There are two types of heaving:

  Sustained heave: It is forceful apex beat that is prolonged and is seen in left ventricular hypertrophy or pressure overload such as aortic stenosis, hypertension and coarctation of aorta.

  Ill- sustained heave: It is a forceful apex beat that is short in duration. It is seen in dilated heart or volume overload such as aortic regurgitation and mitral regurgitation.

Left parasternal or right ventricular heave

Palpate with the heel of hand rested just to the left of sternum with the fingers lifted slightly off the chest for a left parasternal impulse which indicates right ventricular hypertrophy or severe left atrial enlargement.

Thrill

- Thrill is a palpable murmur; it is felt as the purring of a cat and is best felt with distal palm of hand.
- Thrill is palpable when murmur is of grade 4.
- Thrill should be timed into systolic or diastolic by the simultaneous palpation of carotid.
- The most commonly detected systolic thrill is that of aortic stenosis which may be palpable at the apex, left or right sternal edge or over the carotid arteries. The thrill arising from VSD is usually best felt at the left sternal edge.
- Diastolic thrill are rare.
- Thrills are palpable over the base of the heart (the upper part of the chest that includes aortic and pulmonary areas) due to underlying lesion and are best felt with the patient sitting up, leaning forward and in full expiration. In this position base of the heart is moved closer to the chest wall.

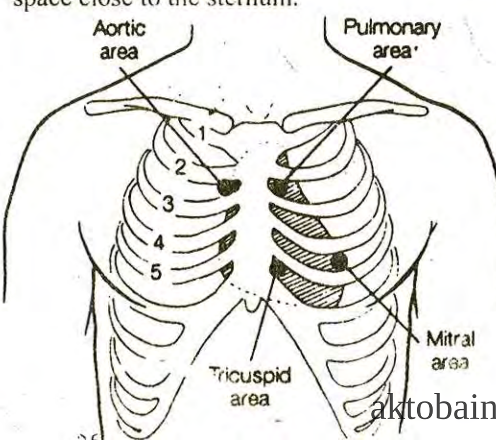
Palpable heart sound

Palpation with the finger over the pulmonary area may reveal the palpable P2 in case of pulmonary hypertension.

AUSCULTATION

Areas of auscultation

- **Mitral area**: At apex.
- **Tricuspid area:** Fifth left intercostals space, close to the lower part of sternum.
- **Pulmonary area:** Left second intercostals space close to the sternum.
- **Aortic areas:** There are two aortic areas A_1 in the right second intercostals space close to the sternum while A_2 in the left third intercostals space close to the sternum.



Scheme of auscultation

- Auscultation of the heart begins in the mitral area with the bell of stethoscope. The bell is particularly efficient in amplifying low-pitched sounds such as diastolic murmurs of mitral stenosis and third heart sound. (use bell when patient is properly exposed otherwise use diaphragm).
- Next auscultate the mitral area with the diaphragm of the stethoscope, which is particularly useful in amplifying high pitched sounds such as systolic murmur of mitral regurgitation or a fourth heart sound.
- Then place the stethoscope in the tricuspid area (fifth left intercoastal space) and auscultate with diaphragm.
- Now auscultate pulmonary area (second left intercostals space) with diaphragm.
- Auscultate aortic area in right second intercostals space with diaphragm and then second aortic area in left third intercostals space.

Summary of the auscultation procedure

The mitral, tricuspid, pulmonary and aortic areas should be auscultated in turn.	**Sitting forward** Aortic diastolic murmur
Supine *First heart sound* Mitral area	**Lying on the left side** Mitral diastolic murmur on mitral area (exactly over the apex best)
Second heart sound Pulmonary and aortic areas, during inspiration and expiration	**During inspiration and expiration** Left sided murmur increase on expiration while the right sided increase on inspiration.
Third and fourth heart sounds Mitral and tricuspid areas.	**Exercise, Valsalva maneuvers** Can be used to accentuate murmurs.
Click, snaps Mitral and tricuspid areas	
Systolic murmurs All four auscultation areas, also the neck, axilla and back.	

Use of the stethoscope	
Bell For low-frequency sounds	**Diaphragm** For high-frequency sounds
Mid-diastolic rumbles of mitral stenosis and tricusid stenosis	Early diastolic murmurs of aortic and pulmonary regurgitation
Third and fourth heart sounds	Second heart sound Systolic clicks and opening snaps.

OBJECT OF AUSCULTATION

- First and second heart sound
- Extra heart sounds (third and fourth)
- Additional sounds (opening snap, ejection click)
- Pericardial rub.
- Murmurs.

HEART SOUNDS

First heart sound

First heart sound is produced by the closure of mitral and tricuspid valve. It is best heard at the apex. Causes of variability are following:

Loud first heart sound

- Mitral stenosis
- Tricuspid stenosis
- Tachycardia
- Increased cardiac output

Soft (quiet) first heart sound

- Mitral regurgitation
- First degree heart block
- Left bundle branch block

Second heart sound

Loud aortic (A2)

- Congenital aortic stenosis
- Systemic hypertension

Soft aortic (A2)

- Aortic regurgitation
- Calcified aortic valve.

Loud pulmonary (P2)

Pulmonary hypertension

Soft pulmonary (P2)

Pulmonary stenosis

Splitting of second heart sound

Normally aortic valve closes earlier than pulmonary valve causing splitting of sound into two components A2 and P2. This splitting is more prominent during inspiration and narrows during expiration. Abnormalities of splitting may be as follow:

Wide splitting (increased normal splitting)

It results from delay in right ventricular emptying that occurs in:

- Right bundle branch block
- Pulmonary stenosis
- Pulmonary hypertension
- Ventricular septal defect
- Mitral regurgitation

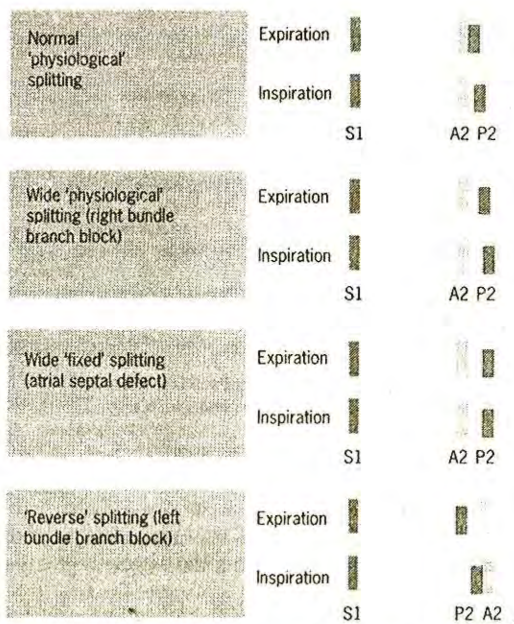
Fixed splitting (no respiration variation)

- Atrial septal defect.

Reversed splitting

P2 occurs first and splitting occurs in expiration. It results from delayed aortic valve closure that occurs in:

- Aortic stenosis
- Coarctation of aorta
- Left bundle branch block
- Large patent ductus arteriosus
- Hypertrophic cardiomyopathy



Variations of the second heart sound. S1, first heart sound; A2, aortic component; P2, pulmonary component.

Third heart sound (S3)

Physiological 3rd heart sound

It is a filling sound that results from rapid diastolic filling as occurs in:

- Healthy young adults
- Children
- Atheletes
- Pregnancy
- Fever

Pathological 3rd heart sound

Third heart sound is a mid-diastolic sound. It results from reduced ventricular compliance so that a filling sound is produced. Third heart sound along with tachycardia is heard like galloping of horse and is called gallop rhythm.

Left ventricular S3

- Left ventricular S3 is louder at apex and with expiration.
- It can be physiological under the age of 40 years, otherwise it is an important sign of left ventricular failure, but it may also occur in aortic regurgitation, mitral regurgitation, VSD and PDA.

Right ventricular S3

- Right ventricular S3 is louder at the left sternal edge and with inspiration.
- It occurs in right ventricular failure or constrictive pericarditis.

Fourth heart sound (S4)

The fourth heart sound is a late diastolic sound and is responsible for gallop rhythm. It is never physiological and is caused by forceful atrial contraction as a result of poor ventricular compliance. It is best heard with the bell of the stethoscope at the apex.

Left ventricular S4

Left ventricular S4 occurs whenever left ventricular compliance is reduced due to aortic stenosis, acute mitral regurgitation, systemic hypertension, ischemic heart disease or advanced age. It is often present during an episode of angina or with a myocardial infarction.

Right ventricular S4

Right ventricular S4 occurs when right ventricular compliance is reduced in pulmonary hypertension or pulmonary stenosis.

Summation gallop

When the heart rate is more than 120 per minute, S3 and S4 may be superimposed resulting in summation gallop in which two sounds may combine to produce one sound.

ADDED SOUNDS

Opening snap

This sound is produced by sudden opening of stenosed mitral valve and heard during early diastole, followed by a mid-diastolic murmur of mitral stenosis. It is only audible when the valve is mobile. Opening snap is best heard at the apex.

Ejection click

It is an early systolic sound heard over the aortic or pulmonary area due to opening of stenosed aortic or pulmonary valve. It is followed by the systolic ejection murmur of aortic or pulmonary stenosis.

Midsystolic click

It is a high pitched sound heard during systole at apex resulting from mitral valve prolapse.

Pericardial rub

It is a feature of pericarditis and is best heard by diaphragm of stethoscope at the left of the lower sternum with the patient breathing out. This scratching sound has both systolic and diastolic components.

MURMURS

These are abnormal sounds produced by turbulent blood flow in the heart caused by:

- Abnormal valve function; stenosis or regurgitation.
- Increased volume or velocity of blood flowing through a normal valve such as during pregnancy, severe anemia and in athletes.
- Flow of blood through communications such as ASD, VSD.

CHARACTERISTICS OF HEART MURMURS

1. Timing: systolic or diastolic
2. Duration: e.g. pansystolic or mid-systolic
3. Site of maximum intensity.
4. Radiation
5. Grading: there are six grades of intensity
6. Character
7. Relation with posture
8. Relation with respiration.

When you describe murmur always tell all characters of murmur to the examiner.

Timing of murmur

Most heart murmurs are either systolic or diastolic, however they can coexist and need to be differentiated by palpating the carotid pulse during auscultation.

- *Systole (pronounce sistlee)* starts with the first heart sound (coincides with the carotid pulse) and ends on second heart sound. Murmurs heard during this period are called systolic murmurs.
- *Diastole (pronounce diastlee)* is the interval between second and first heart sound and it does not coincide with the carotid pulse. Murmurs heard during this period are called diastolic murmurs.

Duration of murmur

Murmurs may be mid-systolic or pansystolic, early diastolic or mid- diastolic. This identification of duration of murmurs is helpful in the diagnosis.

Area of maximum intensity

Murmur may be audible all over the precordium but the maximum intensity of murmur is heard where it originates e.g. murmur of mitral regurgitation are loudest at the apex (mitral area) radiating to axilla but may be heard widely over the precordium and even up into the aortic area or over the back.

Radiation

Murmurs radiate in the direction of blood flow to the specific sites from the precordium. Usually the *systolic murmur radiates.* When the area of maximum intensity has been noted, the stethoscope should be moved radically from this point in different directions to observe whether the murmur is localized or radiating to other parts of chest wall. For example systolic murmur of mitral regurgitation radiates to axilla and round to the back, systolic murmur of aortic stenosis radiates to the carotid arteries in the neck. Systolic murmur of VSD often radiates up to the left sternal border.

The murmur of mitral stenosis and of tricuspid stenosis or regurgitation tends to be localized (all are diastolic murmurs)

Grading of murmur

There are six grades of murmur intensity or loudness as following:

Grade	Features
Grade 1/6	So faint or soft that it is heard only with special effort.
Grade 2/6	Soft, but can be detected almost immediately by an experienced auscultator
Grade 3/6	Prominent but not loud; no thrill
Grade 4/6	Loud; thrill just palpable
Grade 5/6	Very loud, heard even half of diaphragm is removed from contact with chest wall; thrill easily palpable
Grade 6/6	Very loud, can be heard when diaphragm of stethoscope is just removed from contact with the chest wall.

Character

Murmurs of stenosis are usually harsh and murmurs of regurgitation are blowing in character.

Dynamic maneuvers

All patients with newly diagnosed murmur should undergo dynamic maneuvers as following:

Relation with respiration

Murmurs of left side become louder during expiration and murmurs of right side become louder during inspiration.

Relation with posture

Diastolic murmur of mitral stenosis is best heard in left lateral position while the diastolic murmur of aortic regurgitation is best heard when the patient sits and leaning forward.

Dynamic maneuvers and systolic murmurs

Manoeuvre	Hypertrophic cardiomyopathy	Mitral prolapse	Mitral regurgitation	Aortic stenosis
Valsalva's Manoeuvre	Louder	Longer	Softer	Softer
Squatting	Softer	Shorter	Louder	Louder
Hand grip	Softer	Shorter	Louder	Softer

Valsalva's maneuver

This is a forceful expiration against a closed glottis. Ask the patient to hold the nose with his or her fingers, close the mouth, breath out hard so as to pop the eardrums, and hold this as long as possible. Listen over the left sternal border during the maneuver for changes in systolic murmur of hypertrophic cardiomyopathy, and over the apex for changes when mitral valve prolapse is suspected.

Squatting

Squatting increases venous return and increases stroke volume leading to loudness of most of the murmurs.

Hand grip

Sustained handgrip for 20-30 seconds increases systemic arterial resistance, blood pressure and heart size leading to softening of murmur of aortic stenosis and hypertrophic cardiomyopathy while murmur of mitral regurgitation becomes louder.

Functional (innocent) murmurs

These systolic murmurs are produced due to change in the velocity or viscosity of blood. These murmurs are present in the absence of heart abnormalities, disappear on exercise, do not radiate, thrill is never present and there is no change in the loudness of murmur with change of posture or respiration.

Causes are:

- Anemia, polycythemia
- Fever
- Cirrhosis
- Thyrotoxicosis
- Hypertension

MURMUR	POSITION WHERE MURMUR IS BEST HEARD
SYSTOLIC	
Ejection (mid) systolic	
• Aortic stenosis	• Aortic area
• Pulmonary stenosis	• Left sternal border
• Atrial septal defect	• Left sternal border
• Hypertrophic cardiomyopathy (HOCM)	• Left sternal border
• Fallot's tetralogy	• Left sternal border.
Pan-systolic	
• Mitral regurgitation	• Apex
• Tricuspid regurgitation	• Left sternal border
• Ventricular septal defect	• Left sternal border
Late systolic	
• Hypertrophic cardiomyopathy (HOCM)	• Accentuated on standing
• Mitral valve prolapse	• Apex
• Coarctation of aorta	• Left sternal border
DIASTOLIC	
Mid-diastolic	
• Mitral stenosis	• Apex, patient on left side, accentuated on exertion
• Tricuspid stenosis	• Left sternal border, accentuated on inspiration
• Austin-Flint murmur	• Apex

Early diastolic	
• Aortic regurgitation	• Left sternal border (third intercostals space second aortic area and apex, patient sitting forward and in expiration.
• Pulmonary regurgitation	• Right of sternum, louder on inspiration
• Graham – Steel in pulmonary hypertension (due to mitral stenosis	• Left sternal border

Combined systolic and diastolic	
• PDA • Aortic stenosis and regurgitation.	Left sternal border

VALVULAR HEART DISEASE

Chronic valvular heart disease develops in at least half of those affected by rheumatic fever with carditis. The predominantly affected valve is the mitral (in > 90%) and then less commonly the aortic, tricuspid and pulmonary Valvular heart disease develops after several years of onset of rheumatic fever. A diseased valve may be narrowed (stenosis) or it may fail to close adequately (regurgitation).

Exam Tips:

- Patients kept for short cases in examination may have more than one valve involvement and there may be both components stenosis and regurgitation. However first consider involvement of mitral and aortic valve because involvement of tricuspid and pulmonary valve is usually secondary to pulmonary hypertension as result of involvement of mitral valve. In case of multiple lesions decide which one is predominant. Your patient may have congenital heart disease such as ASD, VSD, Tetralogy of Fallot.
- Describe that you can defend. Sometimes colleagues help you by telling the diagnosis, remember! that diagnosis is echocardiography based, you may find clinical features different from that diagnosis. Therefore describe that you feel, don't worry about the accurate diagnosis; this is the exam of clinical methods, logical defense and the best description of your findings.
- After examination of precordium always perform relevant general physical examination.

RHEUMATIC VALVULAR LESIONS	
Valves involved	**% of cases**
• Mitral valve alone	50
• Mitral and aortic valves	40
• Mitral, aortic and tricuspid	5
• Aortic valve alone	2
• All other combinations	3

MITRAL STENOSIS (MS)

ETIOLOGY

- Almost all mitral stenosis is due to rheumatic heart disease.
- At least 50% of the patients have a history of rheumatic fever; some episodes of rheumatic fever may pass unrecognized.
- Rheumatic mitral stenosis is much more common in women (about two- third cases).
- Rare causes of mitral stenosis may be congenital, or because of calcification and fibrosis of the valve in elderly.

PATHOPHYSIOLOGY

Rheumatic fever results in four forms of fusion of the mitral valve apparatus leading to stenosis:

1. Commisures of mitral valve
2. Cusps
3. Chordae tendinae
4. Combined.

The normal mitral valve orifice is about 4-6 cm^2 in diastole; it is reduced to about 1 cm^2 in severe mitral stenosis. With the reduction in the size of the valve orifice, blood can flow from the left atrium to the left ventricle only if propelled by the rise in left atrial, pulmonary venous and pulmonary capillary pressures (producing pressure gradient), with resulting loss of lung compliance and development of exertional dyspnea. This dyspnea is precipitated by tachycardia resulting from exercise, sexual intercourse, infection or atrial fibrillation, all of which increase the rate of blood flow across the

mitral orifice and result in further elevation of laft atrial pressure.

With gradual rise in pressure, there tends to be an increase in pulmonary vascular resistance which protects against pulmonary edema but causes pulmonary hypertension while sudden increase in pulmonary venous pressure caused by atrial fibrillation may precipitate pulmonary edema.

- In about 80% of cases left atrial dilatation is prominent. In a minority, left atrium remains small but becomes hypertrophied.
- All cases may develop pulmonary hypertension and right ventricular hypertrophy.
- All patients with mitral stenosis are at risk of left atrial thrombosis and systemic thromboembolism, particularly those patients with atrial fibrillation.
- Mitral stenosis is frequently associated with mitral regurgitation or disease of the aortic or tricuspid valve.
- When rheumatic fever results exclusively or predominantly in contraction and fusion of the chordae tendineae with little fusion of valvular commissures, dominant mitral regurgitation results.

CLINICAL FEATURES

SYMPTOMS

Exertional dyspnea

Progressively severe dyspnoea results from pulmonary venous hypertension and reduced pulmonary compliance. Dyspnea may be accompanied by cough and wheezing. Vital capacity is reduced due to presence of engorged pulmonary vessels and interstitial edema. Attacks of pulmonary edema may be precipitated by tachycardia. Recurrent chest infections are common.

Hemoptysis

Several types of hemoptysis are seen in patient of MS.

- *Sudden hemorrhage:* Profuse bleeding due to rupture of thin-walled dilated bronchial veins due to sudden rise in left atrial pressure.
- *Blood-stained sputum* with attacks of
- *Blood -stained frothy sputum* characteristic of pulmonary edema with rupture of alveolar capillaries.
- *Blood -stained sputum complicating chronic bronchitis* as the congested mucosa is prone to chronic bronchitis.

Chest pain

Chest pain similar to angina occurs in some patients of MS due to severe right ventricular hypertension secondary to pulmonary vascular disease. Chest pain may also occur due to coronary artery embolism leading to angina or MI.

Palpitation

Large left atrium favors atrial fibrillation resulting in palpitation.

Systemic embolization

Atrial fibrillation may result in systemic and pulmonary emboli which give rise to cerebral, mesenteric, renal and coronary infarctions.

Right heart failure

Right heart failure develops due to pulmonary hypertension and increased pulmonary vascular resistance manifesting as hepatomegaly, edema, ascites and pleural effusion.

Hoarseness

Compression of large recurrent laryngeal nerve by greatly dilated left atrium, enlarged tracheobronchial lymph nodes and dilated pulmonary artery may cause hoarseness.

Symptoms of mitral stenosis

- Exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea.
- Hemoptysis
- Chest pain
- Palpitation
- Hoarseness
- Right heart failure

STAGES OF MITRAL STENOSIS		
Class	**Valve area (cm^2)**	**Symptoms**
Minimal	> 2.5	None
Mild	1.4-2.5	Minimal dyspnea with marked exertion
Moderate	1.0-1.4	Dyspnea, orthopnea, paroxysmal nocturnal dyspnea, pulmonary edema
Severe	<1.0	Resting dyspnea, NYHA class IV
With pulmonary hypertension	<1.0	As in severe plus right ventricular failure

ON EXAMINATION

Inspection of Precordium

Left parasternal pulsation is seen due to right ventricular hypertrophy or forward displacement of the heart by a dilated left atrium.

Palpation

1. Apex beat is not displaced.
2. Tapping apex beat: First heart sound may become palpable (taping apex beat) due to the closures of the stenosed valve with unusually loud sound.
3. Left parasternal heave may be felt due to right ventricular hypertrophy.
4. Palpable P2 in case of pulmonary hypertension.
5. Diastolic thrill at apex (in left lateral position)

Auscultation

Heart sounds

- Loud first heart sound, if valve is pliable (no loud first heart sound if valve is fibrotic or calcified). Pliable means flexible, mobile, non-fibrotic non- calcified.
- Loud P2

Added sounds

- Opening snap

Murmurs

- Mid-diastolic rumbling murmur (best heard with the bell of the stethoscope with the patient in left lateral position). The length of the murmur is proportional to the severity of mitral stenosis. Murmur may become loud if patient exercises prior to auscultation.
- In so-called *silent MS*, there is usually marked right ventricular enlargement, therefore right ventricle occupies the cardiac apex, the left ventricle is rotated posteriorly, so that the murmur is not audible at all or can be heard only in mid or posterior axillary line.
- Pre-systolic accentuation of murmur.

General physical examination

Malar flush: Patients with severe MS, low cardiac output, and systemic vasoconstriction may develop pinkish-purple patches on cheeks called malar flush.

Pulse: pulse is usually normal, may be small in volume due to reduced stroke volume. Rhythm may be irregularly – irregular due to atrial fibrillation).

JVP: prominent *a* wave in patient with sinus rhythm due to forceful right atrial contraction, In atrial fibrillation *x* descent disappears and prominent 'v' wave due to tricuspid regurgitation.

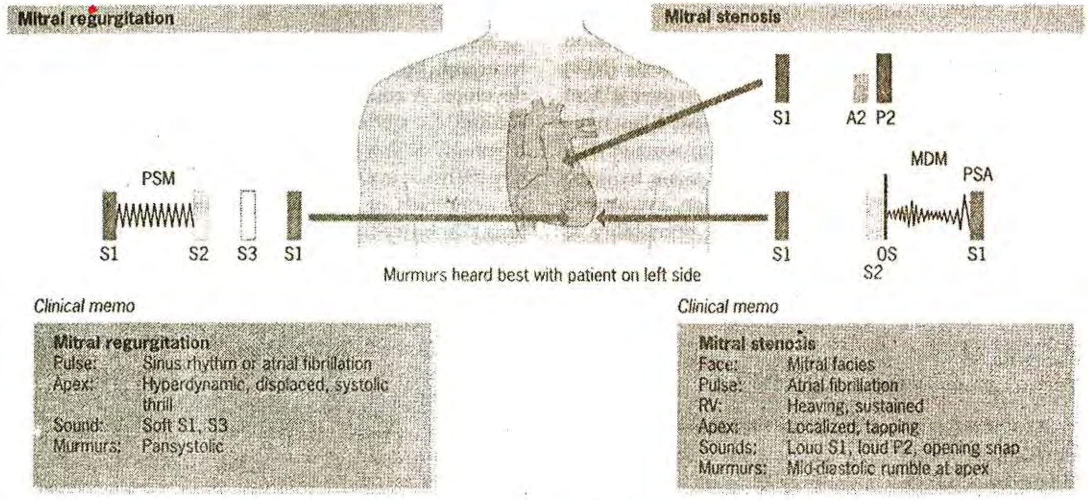
Other findings may be present

Along with above features following findings may be present.

1. Pansystolic murmur: Along the left parasternal border due to tricusid regurgitation as a result of right ventricular dilation.
2. Graham-Steel murmur: This is an early diastolic murmur heard at pulmonary area due to functional pulmonary regurgitation as a result of pulmonary hypertension.
3. Pan systolic murmur: at apex in case there is mitral regurgitation present along with mitral stenosis

ASSESSMENT OF SEVERITY OF MS

- *Echocardiography based:* Severity of mitral valve is usually assessed by measuring mitral valve area, pressure gradient across the mitral valve and presence of pulmonary hypertension. This assessment requires echocardiography.



Auscultatory features associated with mitral regurgitation and mitral stenosis. A2, aortic component of the second heart sound; MDM, mid-diastolic murmur; OS, opening snap; P2, pulmonary component of the second heart sound; PSA, presystolic accentuation; PSM, pansystolic murmur; S1, first heart sound; S2, second heart sound; S3, third heart sound.

- *Clinically* we can assess the severity of MS by the following features:
  - *Opening snap closer* to second heart sound.
  - *Length of mid- diastolic murmur*; the murmur may become quieter in late stages due to reduction of cardiac output.
  - *Loud first heart sound becomes softer* if the valve is not pliable (becomes immobile due to calcification).

DESCRIPTION OF FINDINGS

- *Loud first heart sound:* Because the cusps are kept open until the beginning of ventricular systole. First heart sound becomes soft when the valve becomes immobile due to calcification.
- *Opening snap:* This occurs owing to forceful opening of the valve by raised pressure in the left atrium. The closeness of opening snap to the second heart sound is proportional to the severity of the mitral stenosis.
- *Mid-diastolic murmur:* The murmur is owing to turbulent blood flow through the narrowed valve. This is localized and low pitched so this is heard better with the bell (than diaphragm) while the patient is in left lateral posture. The length of murmur is proportional to the severity of the mitral stenosis.
- *Pre-systolic accentuation of the murmur:* The murmur becomes louder at the end of diastole due to left atrial forceful contraction; however no accentuation if patient is in atrial fibrillation (because no effective atrial contraction occurs in atrial fibrillation).
- *Loud P-2*: It is heard at pulmonary area. P-2 becomes louder due to pulmonary hypertension.

SIGNS OF PULMONARY HYPERTENSION

- Right ventricular heave due to right ventricular hypertrophy.
- Loud P2
- Right heart failure.
- Pulmonary valvular regurgitation causing an early diastolic murmur in the pulmonary area called **Graham – Steell murmur.**

COMPLICATIONS OF MITRAL STENOSIS

- Atrial fibrillation
- Systemic embolization
- Pulmonary hypertension
- Pulmonary infarction
- Chest infections
- Infective endocarditis (rare)
- Tricuspid regurgitation
- Rlight ventricular failure.

SAMPLE DESCRIPTION OF MITRAL STENOSIS IN VIVA

- Young female, lying comfortably on bed.
- Inspection of precordium not allowed.
- On palpation apex beat is not displaced, it is in 5th intercostals space 9 cm from the midsternal point. It is tapping in character along with diastolic thrill. Left parasternal heave is also present. P2 is palpable.
- Auscultation reveals loud first heart sound, loud P2, there is opening snap and a mid-diastolic murmur of grade 4/6, harsh, best heard at apex, localized, increased on expiration and decreased on inspiration. The murmur becomes louder in late diastole (pre-systolic accentuation). There is also a diastolic murmur at pulmonary area called Graham- Steell murmur due to functional pulmonary regurgitation as a result of pulmonary hypertension.
- Fine crepts in lung bases.
- There is no hepatosplenomegaly.
- Pulse is of low volume and irregularly irregular due to atrial fibrillation.
- BP is 90/60 mmHg
- JVP is raised.
- Patient is afebrile
- Based on the above evidence on examination my diagnosis is mitral stenosis with pulmonary hypertension.

Please note

Prepare this type of descriptions for other valvular lesions and try to remember them because you have just 5 min for examination of patient in short case. Always tell the examiner in the same way to get good marks.

INVESTIGATION

X-ray chest:

This shows following changes (Mitralization)

- Small heart with an enlarged left atrium which may be visible as a double shadow behind right border of the heart.
- Straightening of left border of the heart
- Prominent pulmonary veins and lung marking.
- Presence of Kerley's B lines – which are small (1-2 cm) horizontal lines present in the costophrenic angles appearing due to raised pulmonary venous pressure and interstitial edema.

ECG:

- Bifid P wave (wide and notched P wave) called P-mitral in lead II indicates left atrial enlargement.
- Right ventricular hypertrophy – (Right axis deviation and tall R wave in lead VI and deep S wave in lead V6) may be present.
- Atrial fibrillation may be present.

Echocardiography

- It confirms the diagnosis and measures the assessment of severity, pliability of leaflets, extent of valvular calcification, fusion of chordae tendineae. The valve is thickened, calcified, stenotic with fusion of mitral valve leaflets and poor leaflet separation during diastole. In mild MS in which some leaflet mobility is preserved, the anterior leaflet may demonstrate *diastolic doming*.
- Left atrium is usually enlarged. Left ventricular cavity may be normal or small.
- Pulmonary artery pressure can be measured by Doppler echocardiography.
- It can also detect thrombosis in the left atrium, however transesophageal echo (TEE) is more sensitive in detection of thrombus in left atrium.

MANAGEMENT

Patients with minor symptoms should be treated medically, but the definitive treatment is surgical. In most cases, there is a long asymptomatic phase, followed by shortness of breath and limitation of activity. Pregnancy and atrial fibrillation precipitate more severe symptoms. There are 4 ways of treatment:

1. Medical treatment
2. Percutaneous balloon mitral valvotomy
3. Surgical valvotomy
4. Surgical valve repair or replacement

MEDICAL TREATMENT

Mild dyspnea: salt restriction, low doses of diuretics.

Patient with sinus rhythm: Beta-blockers to reduce heart rate if patient in sinus rhythm and there is no left ventricular dysfunction. Anticoagulation in sinus rhythm is indicated if there is previous embolic event or left atrial size is > 55 mm on echocardiography.

Patient with atrial fibrillation (AF):

- The rate control may be achieved by using beta- blocker, calcium channel blocker or digoxin (0.125 – 0.25 mg/day).
- Conversion to and subsequent maintenance of sinus rhythm is most successful when the duration of atrial fibrillation is brief (< 6-12 months) and the left atrium is not severely dilated (diameter < 45 mm). AF is poorly tolerated by MS patient. If electrical or pharmacological cardioversion (with amiodarone) is planned in patient who has had AF for more than 24 hours, anticoagulation with warfarin for more than 3 weeks should be performed before cardioversion. Alternatively perform TEE, if no thrombus in left atrium immediate cardioversion may be carried out using intravenous heparin.
- Once atrial fibrillation occurs, the patient should receive warfarin anticoagulation therapy even if sinus rhythm is restored, since 20-30% of these patients will have systemic embolization if untreated.
- Prophylactic antibiotics to prevent infective endocarditis.
- Prophylactic treatment (Inj. Penidure LA 1.2 million units IM after every 3 weeks) to prevent recurrence of rheumatic fever because prevention of repeated attacks may delay the progression of mitral stenosis.
- In pregnancy beta blockers and diuretics may be used to control heart rate and lung congestion. Warfarin should be avoided; heparin may be used for anticoagulation.

PERCUTANEOUS TRANSLUMINAL MITRAL COMMISSUROTOMY (PTMC)

This is also called percutaneous mitral balloon valvotomy. This is the treatment of choice if the appropriate criteria are fulfilled. A catheter is introduced into the right atrium via the femoral vein. The interatrial septum is then punctured and the catheter advanced into the left atrium and across the mitral valve. A balloon is passed over the catheter across the valve, and then inflated briefly to split the valve commissures. The procedure is performed under local anesthesia. Significant valve regurgitation may be the complication necessitating valve replacement. Single or double – balloon may be used. A reusable metallic valvotomy device may be used instead of balloon that reduces the cost of the procedure.

Criteria for selection of patient for PTMC

- Symptomatic patient
- Moderate to severe mitral stenosis
- Pliable leaflets (mobile, non- fibrotic, non-calcified)
- Isolated mitral stenosis, no or mild mitral regurgitation
- Left atrium free of thrombus
- It is also indicated in mild MS if patients are symptomatic during ordinary activity or in asymptomatic patients with moderate to severe MS who develop pulmonary hypertension.

SURGICAL MANAGEMENT

There are 4 surgical options:

- Closed valvotomy
- Open valvotomy
- Mitral valve repair
- Mitral valve replacement (MVR)

Closed valvotomy

Closed valvotomy is performed without the aid of a cardiopulmonary bypass. The surgeon enters the heart using either transatrial or transventricular route. A dilator is introduced without direct visualization. The fused cusps are forced apart by a dilator. This operation is advised for patients with mobile non-calcified and non-regurgitant mitral valves. PTMC has replaced this procedure now. Closed valvotomy may produce a good result for 10 years or more. The valve cusps often refuse and eventually another operation may be necessary.

Open Valvotomy:

In this procedure cardiopulmonary bypass is required. The cusps are carefully dissected apart under direct vision and is effective in those patients who have mitral stenosis with calcified valve or with left atrial thrombus. Thrombi are also removed from left atrium. Chances of mitral regurgitation are less as compared to closed valvotomy however the cost becomes higher.

Mitral valve replacement (MVR)

Mitral valve replacement (MVR) is indicated in:

- Moderate mitral stenosis (mitral valve area <1.5 cm^2) and New York Heart Association class III or IV (dyspnea on mild exertion or at rest) who are not candidate for PTMC or valve repair (badly diseased or badly calcified stenotic valve that can not be reopened without producing significant regurgitation.).
- Severe MS (mitral valve area <1.0 cm^2), functional class II and severe pulmonary hypertension.
- If mitral regurgitation is also present.
- If thrombus in left atrium despite anticoagulation.

Perioperative mortality rate for MVR is less than 5% in young healthy individuals and 20% in older patients who are in functional class IV (This data is Western; mortality is higher in Pakistan). Usually mortality is related to left ventricular dysfunction; (plus related to surgeon's skill and postoperative care) therefore surgery should be performed prior to development of left ventricular dysfunction. Life-long anticoagulation is required and monitoring of anticoagulation in rural patients is also a problem (sometimes they present with massive bleeding, especially intracerebral hemorrhage).

MITRAL REGURGITATION (MR)

ETIOLOGY

Chronic mitral regurgitation

1. Rheumatic heart disease (50%)
2. Mitral valve prolapse (second common cause)
3. Disease that cause dilation of the left ventricle cavity may cause dilatation of valve annulus and mild mitral regurgitation (called functional MR), such diseases are:
    - Aortic valve disease
    - Acute rheumatic fever
    - Myocarditis
    - Dilated cardiomyopathy
    - Hypertensive heart disease
    - Ischemic heart disease.

Less common causes

1. Connective tissue disorder e.g. SLE, rheumatoid arthritis.
2. Hypertrophic cardiomyopathy.
3. Collagen abnormalities e.g. Marfan's syndrome, Ehlers – Danlos syndrome.

Acute mitral regurgitation

1. Myocardial infarction (due rupture of chordae tendineae).
2. Infective endocarditis.

Note: Causes of mitral and aortic regurgitation are the favorite questions of examiners.

PATHOPHYSIOLOGY

- Regurgitation into the left atrium produces left atrial dilatation.
- Left atrial pressure increases slightly if the regurgitation is long standing because regurgitant flow is accommodated by the large left atrium. When regurgitation is acute, the normal compliance of the left atrium does not allow much dilatation and the left atrial pressure rises, which inturn increases pulmonary venous pressure resulting in pulmonary edema.
- Atrial fibrillation is common due to atrial dilatation. Since a proportion of stroke volume is regurgitated, the stroke volume increases to maintain the forward cardiac output and the left ventricle therefore enlarges.
- Mitral regurgitation, like mitral stenosis, predisposes to atrial fibrillation; but thromboembolism is less common, however infective endocarditis is much more common.

SYMPTOMS

Chronic progressive

- Palpitation: due to increased stroke volume and due to atrial fibrillation.
- Exertional dyspnea and then progressing to paroxysmal nocturnal dyspnea and finally orthopnea due to pulmonary venous hypertension.
- Fatigue and lethargy due to reduced cardiac output.
- Hemoptysis and systemic embolization are less common than in MS.

- Symptoms of right heart failure such as ankle edema, abdominal swelling due to ascites. In later stages, features of congestive cardiac failure are present.

Acute

Symptoms of acute pulmonary edema and reduced cardiac output (shock).

ON CVS EXAMINATION

Inspection of precordium

- Apex beat may be visible outside the midclavicular line (displaced) as a result of dilatation of left ventricle.
- Parasternal impulse due to left atrial enlargement.

Palpation

1. Apex beat is displaced laterally and downwards.
2. Apex beat is heaving in character due to left ventricular dilatation.
3. Systolic thrill may be palpable at apex.
4. Palpable P2 in case of pulmonary hypertension.

Auscultation

1. First heart sound (SI) is soft, due to incomplete apposition of the valve cusps.
2. A loud third heart sound (S3) may be present due to sudden rush of blood back into the dilated left ventricle in early diastole.
3. Pansystolic murmur at the apex, radiating widely over the precordium and axilla – produced due to regurgitation occurring throughout the whole systole.
4. Auscultation of lung bases may reveal crepitation, if patient is in failure.

General physical examination related to MR

- **Pulse:** carotid pulse is brisk (sharp) and of low volume, may be irregular due to atrial fibrillation.
- **JVP:** Normal unless right heart failure occurs.
- Signs of atrial fibrillation, pulmonary hypertension and right heart failure may develop later in the disease.
- For the signs of endocarditis, palpate liver and spleen and check temperature.

INVESTIGATIONS

X-ray chest

This shows cardiomegaly due to left atrial and left ventricular enlargement. Pulmonary hypertension may be evident, pulmonary edema and pleural effusion in case of heart failure.

ECG

1. Bifid P wave due to left atrial hypertrophy
2. Left ventricular hypertrophy occurring in about 50% of cases and manifests as:
   - Tall R waves in lead I and V6.
   - Deep S waves in leads VI and V2.
   - Combination of S wave in V1 and R wave in V6 is more than 35 mm.
3. Right ventricular enlargement in some patients.

Echocardiography

This shows dilated left atrium and left ventricle. It confirms the diagnosis of mitral regurgitation.. Severity of MR on echo is estimated by the area and depth of the regurgitant jet into the left atrium. Doppler echocardiography gives better estimate of regurgitation. Echo also helps in identification of etiology of MR.

MANAGEMENT

Medical:

- **Vasodilators** such as ACE inhibitors or hydralazine for acute mitral regurgitation. In asymptomatic chronic MR vasodilators are not beneficial however in mildly symptomatic MR due to left ventricular dysfunction ACE inhibitors may be given. In markedly symptomatic patient surgery is advised.
- **Digoxin** is useful to control heart rate in atrial fibrillation.
- **Diuretics** may be required to reduce lung congestion.
- **Oral anticoagulation** if patient has atrial fibrillation or concomitant mitral stenosis.
- **Antibiotic prophylaxis** against infective endocarditis.

Surgical

Patient usually remains asymptomatic for several years. Mitral valve repair or replacement should be performed earlier before the development of left ventricular dysfunction because patients of left ventricular dysfunction and severe pulmonary hypertension do not achieve symptomatic improvement after surgery.

Indications of surgery in MR:

- Acute MR (urgent surgery)
- Patient becomes symptomatic NYHA functional class II, III, or IV with normal LV function (EF > 60% and endsystolic dimention <45 mm).
- Symptomatic or asymptomatic patients with mild LV dysfunction (EF 50-60%, endsystolic dimention 45-50 mm).
- In symptomatic or asymptomatic patient with moderate LV dysfunction (EF 30-50% and endsystolic dimention 50-55 mm).
- Patient with development of pulmonary hypertension (pulmonary artery systolic pressure > 50 mm Hg) should also be considered for surgery.

Markers of poor prognosis after surgery

- Ejection fraction < 60%.
- End- systolic dimension > 45mm on echo.
- Significant pulmonary hypertension.
- Atrial fibrillation.

MITRAL VALVE PROPLAPSE (MVP)

Mitral valve bulging back into the left atrium during systole is called mitral valve prolapse. This is also called floppy mitral valve or myxomatous mitral valve.

MVP is twice as frequent in women as in men. In the mildest form due to prolapse of mitral valve there is only mid- systolic click but progressively it leads to mitral regurgitation.

MVP exhibits a strong hereditary component and in some patients is transmitted as an autosomal dominant trait.

ETIOLOGY

- Most commonly it develops due to myxomatous degeneration of mitral valve in which middle layer of valve leaflet composed of loose, myxomatous material is unusually prominent.
- Second common cause in our country is rheumatic fever.
- MVP may occasionally result from Marfan syndrome, Ehlers-Danlos syndrome, osteogenesis imperfecta, periarteritis nodosa, myotonic dystrophy, Von-Willebrand disease, hyperthyroidism, Ebstein anomaly of tricuspid valve, hypertrophic cardiomyopathy, ASD II, mitral valve surgery and left ventricular aneurysm.

CLINICAL FEATURES

Symptoms

- Most patients with MVP are asymptomatic.
- In symptomatic patient it presents as chest pain, dyspnea, fatigue, palpitation, syncope and sudden death (reasons of symptoms is unknown). Palpitation may be due to atrial or ventricular premature beats or tachyarrhythmias. Chest pain is similar to angina but may last for hours or days, not related to exertion, and punctuated by brief attacks or severe stabbing pain at the apex. This chest pain or discomfort may be due to abnormal tension on papillary muscles.
- Mitral regurgitaion (MR) may develop due to progressive elongation of chordae tendinae,

- Spontaneous rupture of chordeae tendinae may cause a sudden worsening of MR that is hemodynamically severe.

On examination

- On auscultation there is midsystolic click in mild cases and pansystolic murmur if significant mitral regurgitation. The click is believed to be produced by sudden tensing of the elongated chordae tendineae of prolapsing leaflets. The patient should be examined in supine, left decubitus and sitting positions.
- Thoracic deformities are more prevalent in MVP such as loss of normal thoracic kyphosis (straight back syndrome) pectus excavatum and scoliosis.
- BP may be normal or low.

COMPLICATIONS

- Infective endocarditis
- Rupture of chordae tendineae causing sudden severe MR.
- Progressive MR
- Arrhythmias and sudden death.

INVESTIGATIONS

ECG

ECG may be normal or show arrhythmias such as SVT, atrial or ventricular premature contractions, ventricular tachyarrhythmias, sinus node dysfunction or varying degrees of heart block.

Echocardiography

Echocardiography is diagnostic of MVP. It shows one or both mitral valve leaflets bulging by at least 2 mm into the left atrium during systole. Thickening of the involved leaflet to > 5 mm supports the diagnosis. Doppler echo frequently reveals mild MR that is not always associated with an audible murmur.

MANAGEMENT

- ***Asymptomatic*** patients without arrhythmia on ECG should be reassured about the prognosis and followed every 3-5 years.

- **Beta-blockers** are effective for chest pain, supraventricular tachycardia or frequent ventricular premature beats.

- **Aspirin** is given to patients with MVP who have documented focal neurological deficit.

- **Infective endocarditis prophylaxis** in patients with typical click and systolic murmur and those with only click plus characteristic echo features of MVP.

- Symptomatic ventricular tachycardia requires implantable cardioverter- defibrillator **(ICD).**

- **Surgical treatment** with valve repair or replacement if there is hemodynamically significant mitral regurgitation.

AORTIC STENOSIS (AS)

ETIOLOGY

1. *Rheumatic heart disease* is the most common cause resulting from adhesions and fusions of the commissures and cusps.

2. *Congenitally abnormal (bicuspid) aortic valve.* Normal valve is tricuspid, bicuspid valve may be stenotic with commissural fusion at birth but usually not causing serious narrowing of the aortic orifice during childhood. The abnormal architecture induces turbulent flow, which traumatizes the leaflets and leads to fibrosis, increased rigidity, calcification of leaflets and narrowing of the aortic orifice in adulthood.

3. *Senile AS:* Age related AS degeneration and calcification of previously normal valve in elderly, usually smokers, diabetics, hypertensive and hyperlipidemic.

4. *SLE* and severe familial hypercholesterolemia occasionally cause aortic stenosis.

Other causes of left ventricular outlet obstruction (other than aortic valve stenosis)

- *Subvalvular aortic stenosis:* A congenital condition in which fibrous ridge or diaphragm is situated immediately below the aortic valve causing aortic outflow obstruction.

- *Supravalvular obstruction:* A congenital fibrous diaphragm above the aortic valve often associated with mental retardation and hypercalcemia (Willium's syndrome).
- *Hypertrophic obstructive cardiomyopathy:* Asymmetrical septal hypertrophy obstructing the left ventricular outflow.

PATHOPHYSIOLOGY

- Obstructed left ventricular outflow due to aortic stenosis leads to increased left ventricular pressure and compensatory *left ventricular hypertrophy.* To maintain cardiac output large pressure gradient across the valve is required. Cardiac output at rest is maintained within normal limits in most patients with severe AS, it often fails to rise normally during exertion. Late in the course of the disease, the cardiac output and stroke volume decline (due to LV dysfunction) resulting in decline of pressure gradient across the aortic valve and rise in pulmonary arterial pressure.
- *Ischemia in AS:* Due to hypertrophy, heart requires more blood for oxygenation that may be not be possible in severe AS resulting in myocardial ischemia even in the absence of coronary artery disease. High left ventricular pressure may compress the coronary arteries in systole and shorten the diastolic phase which may lead to reduced coronary blood flow manifesting as myocardial ischemia angina, arrhythmias and left ventricular failure. This ischemia becomes more severe on exercise.

Assessment of severity

Severity of AS is determined by the valve area and the pressure gradient across the valve (usually by echo).

- Normal aortic valve size is 3-4 cm^2.
- Severe AS: Critical obstruction to left ventricular outflow is usually characterized by a peak systolic pressure gradient exceeding 50 mmHg in the presence of a normal cardiac output and aortic valve area less than 0.8 cm^2.
- Moderate AS: Aortic valve area 1.0 -1.5 cm^2
- Mild AS: 1.5-2.0 cm^2

CLINICAL FEATURES

SYMPTOMS

1. Long asymptomatic phase
2. Symptomatic AS manifests as angina, exercise induced syncope, exertional dyspnea and ultimately heart failure and sudden death. These symptoms appear when the aortic orifice is reduced to one-third of its normal size.

Syncope attacks: Syncopal attacks are due to markedly decreased cerebral perfusion that occurs during exertion due to systemic vasodilatation in the presence of reduced cardiac output due to fixed obstruction. Syncope at rest may be due to transient ventricular fibrillation from which patient recovers spontaneously, transient AF, or transient heart block.

Angina pectoris: Angina occurs due to myocardial ischemia which develops when left ventricular oxygen demand exceeds supply i-e decreased coronary blood flow which does not fulfill the requirement of the hypertrophied heart particularly after exercise. Decreased coronary blood flow may be due to compression of coronary arteries by the hypertrophied myocardium. In about 50% of cases, angina is due to significant coronary artery disease.

Exertional dyspnea: Exertional dyspnea, orthopnea and PND are late symptoms in AS and reflect pulmonary venous hypertension

Heart failure: Heart failure occurs due to both left ventricular systolic and diastolic dysfunction.

Gastrointestinal bleeding: GI bleeding may develop in patients with severe AS, often associated with angiodysplasia or other vascular malformations associated with severe AS.

ON CVS EXAMINATION

Inspection of precordium

Apex beat is not displaced, visible on its normal position.

Palpation

- Apex beat is not displaced because hypertrophy (in contrast to dilatation) does not produce cardiomegaly.
- Apex beat is heaving in character (forceful) due to left ventricular hypertrophy (as a result of pressure overload).

- Double apex beat may be palpable due to fourth heart sound or atrial contraction.
- A systolic thrill may be felt in the aortic area or suprasternal notch and is frequently transmitted along the carotid arteries.
- Rarely right ventricular failure with hepatomegaly, and edema precedes left ventricular failure due to hypertrophy of ventricular septum that encroaches the right ventricular cavity causing impairment of right ventricular filling.

Auscultation

Heart sounds

- S1 is normal or soft
- S2 is soft because only P2 is audible while A2 is inaudible due to immobility of aortic valve as a result of calcification.

1. Reversed splitting of second heart sound. Normally during inspiration, splitting of 2nd heart sound becomes wide. But in this case it becomes narrow during inspiration and wide during expiration due to delayed closure of aortic valve.
2. A prominent fourth heart sound.

Added sound

Systolic ejection click

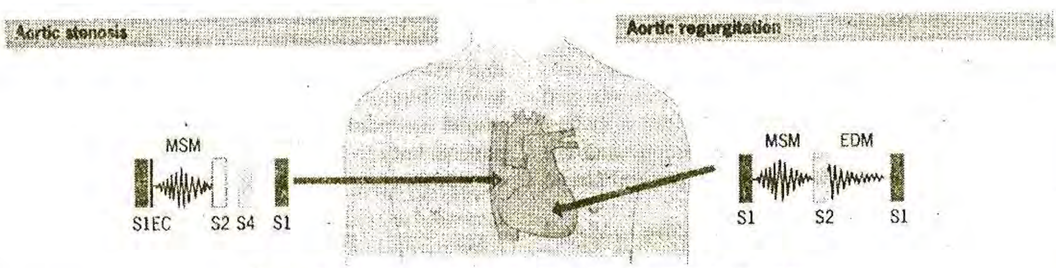
Murmur

Ejection systolic (mid- systolic) murmur

- Ejection systolic (mid- systolic) murmur is present at aortic area. The murmur is usually rough in quality and best heard in aortic area.
- It radiates to the carotid artery and also the precordium to the apex. (it usually produces confusion that patient has two lesions AS and MR; however remember that systolic murmur at apex is murmur of MR that is pansystolic while murmur of AS is mid- systolic).
- The murmur of AS is reduced in intensity when standing due to reduced transvalvular flow.
- Longer the murmur severe is the aortic stenosis. However when the left ventricle fails and the stroke volume falls, the systolic murmur of AS becomes softer; rarely, it disappears altogether.

General physical examination related to AS

- Pulse: carotid pulse is low volume and slowly rising called anacrotic pulse. Simultaneous palpation of the apex and carotid artery reveals delay in carotid pulse in severe AS.
- Pulse pressure: Narrow in late stages
- JVP: prominent a wave due to reduced compliance of right ventricle due to pulmonary hypertension or hypertrophy of the ventricular septum.



Murmurs heard best with patient leaning forwards and breath held in expiration

Clinical memo

Aortic stenosis	
Pulse:	Sinus rhythm, low volume, slow rising
Aortic area:	Systolic thrill
Apex:	Not displaced, sustained
Sounds:	Ejection click, soft A2, S4
Murmurs:	Systolic, low pitched, ejection, radiating to carotids

Clinical memo

Aortic regurgitation	
Pulse:	Sinus rhythm, large volume, collapsing
Blood pressure:	Wide pulse pressure
Apex:	Displaced, diffuse, hyperdynamic
Murmurs:	(1) High pitched, early diastolic at LSE (2) Ejection systolic at base and into neck (3) Mid-diastolic rumble at apex (Austin-Flint)

Auscultatory features of aortic stenosis and aortic regurgitation. EC, ejection click; EDM, early diastolic murmur; .

INVESTIGATIONS

X-ray chest

- Chest X-ray may be normal in critical AS
- The heart is usually normal in size or slightly enlarged.
- Post-stenotic dilatation of ascending aorta on PA view is commonly seen.

ECG

- Left ventricular hypertrophy.
- Left ventricular strain due to pressure overload (such as depressed ST segments and T wave inversion in leads I, AVL, V5 and V6).
- Left atrial enlargement.

Echocardiography

- This shows thickened, calcified and immobile aortic valve cusp.
- Detects left ventricular hypertrophy, its systolic and diastolic function.
- Doppler echocardiography demonstrates the pressure gradient across the valve and the valve area. Gradient more than 50 mmHg or an aortic area less than 0.8 cm^2 indicates that the aortic stenosis is severe enough to cause patient's symptoms. However it should be remembered that patient may become symptomatic at valve area 1 cm and may remain asymptomatic even at valve area 0.6 cm with high systolic pressure gradient.

Cardiac catheterization

Cardiac catheterization is required in patient 40 years and above for coronary angiography and to confirm the gradient across the aortic valve. Coronary angiography is performed to diagnose cause of angina that may be due to coronary artery disease or aortic stenosis. Angiography is indicated in patient aged 40 years or above if valve replacement is planned therefore CABG is performed during the procedure of valve replacement.

TREATMENT

Medical treatment is not effective for aortic stenosis. Patient who develops any of the three symptoms (angina, syncope or heart failure) is the candidate for valve replacement.

- About 50% patients with aortic stenosis who develop *angina* are dead within *5 years* of its onset if valve replacement is not performed.
- About 50% patients with aortic stenosis who develop *syncope* are dead within *3 years* of its onset if valve replacement is not performed.
- About 50% patients with aortic stenosis who develop *heart failure* are dead within *2 years* of its onset if valve replacement is not performed.

Surgery is not indicated for asymptomatic patients except those with declining left ventricular function, very severe left ventricular hypertrophy and very high gradient (>80 mmHg) or severely reduced valve area (< 0.7 cm^2)

Medical management

Medical treatment is given to those patients who are inoperable (usually due to comorbids).

- Avoid strenuous physical activity.
- Carefully follow up of the patient because the disease is progressive; gradient (on echo) increase by 4-8 mmHg per year while the valve area decreases by 0.2-0.3 cm^2 per year. In mild AS, repeat echo every 2 years, in asymptomatic severe AS echo should be done every 6-12 months. ETT may be helpful in asymptomatic patient to detect covert symptoms, limited exercise capacity and abnormal blood pressure response; ETT is contraindicated in symptomatic patients.
- Angina may be treated with beta-blockers but cautiously because they may lead to shock or heart failure.
- Nitrates aggravate exertional syncope and should be avoided.
- ACE inhibitors and digoxin are relatively contraindicated i-e digoxin is indicated if the ejection fraction is reduced and ACE inhibitors in small doses are indicated in patients with symptomatic left ventricular systolic dysfunction who are not candidate for surgery.

Surgical treatment

Valve replacement is indicated early and in following conditions:

- All symptomatic patients including with left ventricular dysfunction that often improves postoperatively.
- Asympyomatic patient with declining left ventricular function, severe left ventricular hypertrophy, severely reduced valve area (< $0.7cm^2$) or a hypotensive response to exercise.
- Patient of severe AS undergoing another cardiovascular operation such as CABG.

INDICATIONS OF SURGERY IN AS

- Symptomatic patients with severe AS.
- Patients with severe AS undergoing CABG or the surgery of aorta or another valve.
- Asymptomatic patients with severe AS with either left ventricular systolic dysfunction or hypotensive response to exercise. Asymptomatic patients with severe AS having marked LV hypertrophy or valve area <0.6 cm^2 may be considered for surgery.

Aortic stenosis with left ventricular dysfunction

Surgical risk is higher in patients with impaired LV function (EF< 35%), however their prognosis is poor without operation, and overall survival is improved with valve replacement.

Aortic stenosis with low gradient

Patients with critical AS and severe LV dysfunction present with not much high pressure gradient across the aortic valve; creating a confusion either it is a cardiomyopathy with calcified non-stenotic valve or AS with severe LV dysfunction. As the gradient and valve area of aortic valve depend on blood flow, to differentiate the two conditions flow across the valve is increased by dobutamine and then gradient and valve area are calculated again. In case of LV dysfunction gradient increases while the valve area remains same whereas in cardiomyopathy calculated valve area increases.

Risk factors that increase mortality in surgery

- Patient highly symptomatic (high NYHA functional class).
- Impaired left ventricular function (EF < 45 or 50%)
- Advanced age
- Presence of associated coronary artery disease

TYPES OF VALVES

Metallic valves: Metallic valves are durable but thrombogenic and need life-long anticoagulation. Metallic valves are used in majority of cases.

Bioprosthetic valves: Bioprosthetic valves are constructed from porcine aortic valve leaflets or bovie pericardium. They do not need anticoagulation but life of valve is short, they degenerate comparatively early; 50% valve fail within 15 years. Valve degenration is more rapid in young population therefore not recommended in less than 35 years of age except for young female who wants to become pregnant (because anticoagulation required for metallic valve with warfarin can not be given during pregnancy due to high fetal mortality)

Aortic balloon valvoplasty

- Percutaneous valvoplasty is effective in children, adolescents and young adults with congenital noncalcified aortic stenosis but it is not much helpful in calcified aortic stenosis that occurs in adults because rate of restenosis from scarring is very high, occurring in about 50% of patients within 6 months.
- Percutaneous aortic balloon valvoplasty can produce short- term reduction in the severity of aortic stenosis in adults who are poor candidate for surgery such patients with cardiogenic shock due to critical AS or with severe heart failure.
- It can also be performed as an intermediate procedure to stabilize high risk patient prior to surgery or if the seriously ill patient requires urgent major non- cardiac surgery.

AORTIC REGURGITATION (AR)

ETIOLOGY

Valvular disease

1. Rheumatic fever (most common cause)
2. Infective endocarditis
3. Bicuspid aortic valve
4. Large VSD
5. SLE
6. Ankylosing spondylitis
7. Rheumatoid arthritis
8. Takayasu disease
9. Whipple disease
10. Crohn disease
11. Appetite suppressing (anorectic) drugs

Aortic root disease (dilatation of ascending aorta)

1. Marfan's syndrome (cystic medial necrosis of aorta)
2. Bicuspid valve
3. Dissection of aorta
4. Syphilitic aortitis
5. Osteogenesis imperfecta
6. Ankylosing spondylitis
7. Bachet syndrome
8. Psoriatic arthritis
9. Reiter's syndrome
10. Giant cell arteritis
11. Arthritis associated with ulcerative colitis
12. Ruptured sinus of Valsalva aneurysm
13. Failure of prosthetic heart valve
14. Severe hypertension.

Causes of acuteAR

- Acute rheumatic fever.
- Infective endocarditis
- Dissection of aorta
- Ruptured sinus of Valsalva aneurysm
- Failure of prosthetic heart valve

PATHOPHYSIOLOGY

During diastole blood is regurgitated from aorta through the aortic valve into the left ventricle. If net cardiac output is to be maintained, the total volume of the blood pumped into the aorta must increase, and consequently the left ventricular size must enlarge. As the blood is refluxed during diastole, the diastolic blood pressure falls and coronary perfusion is decreased. In addition, the larger left ventricular size demands more oxygen which cannot be supplied resulting in cardiac ischemia.

SYMPTOMS OF CHRONIC AR

Asymptomatic patient

Patient remains asymptomatic for a long time during which period left ventricle gradually enlarges.

Symptomatic patient

Symptoms of AR develop late resulting from reduced reserve or myocardial ischemia as a result of cardiomegaly and myocardial dysfunction.

- Angina may be the symptom resulting from concomitant coronary artery disease or low diastolic pressure and increased oxygen demand from ventricular hypertrophy.
- Exertional dyspnea and fatigue are the most common symptoms as a result of failing heart.
- Palpitation due to awareness of forceful left ventricular contraction or premature atrial or ventricular contraction in severe AR.

SYMPTOMS OF AR

Mild AR

- Asymptomatic
- Palpitation due to awareness of heart beat

Severe AR

- Angina
- Dyspnea due to left ventricular failure

ON EXAMINATION

Inspection of precordium

- Prominent pulsation over the precordium
- Apex beat displaced outside the midclavicular line.

Palpation

- Apex beat is diffuse, palpable outward and downward.
- Apex beat heaving in character due to left ventricular hypertrophy.

- A diastolic thrill may be felt at the left sternal border (3rd left space, A2 area). When the patient sits, leans forward and expirates.

Auscultation

Heart sounds

- Soft S1 due to prolonged PR interval
- A2 may be soft or absent, P2 may be obscured by diastolic murmur, therefore S2 may be single or absent.
- S4 is often audible.

Murmur

- Early diastolic murmur best heard at second aortic area (A2), located in left third intercostals space close to the sternum particularly when patient sits, leans forwards and holds his breath after expiration. Prolonged the murmur, severe is the AR.
- A systolic ejection murmur may be present at aortic area due to high flow state.

Other auscultatory findings

- Austin-Flint murmur: It is a mid-diastolic murmur heard at the apex. It is produced as a result of backward leakage of blood from the aortic valve (during diastole) that pushes the anterior leaflet of mitral valve towards mitral opening. It produces a "functional mitral stenosis" producing mid-diastolic murmur.
- Pistol shot femoral: A sharp sound heard on auscultation over the femoral arteries in time with each heart beat.
- Durozier's sign bruit heard over femoral arteries on light compression by stethoscope.

General physical examination related to AR

Features of etiology

Marfan's syndrome, ankylosing spondylitis.

Pulse:

This is of high volume and bounding or collapsing (water-hammer) in character. The following signs which are rare but may be present.

- Quincke's sign: Capillary pulsation in the nail beds.
- De Musset's sign: The carotid pulsations are so forceful that head moves with them, also called nodding of the head.
- Corrigen's sign: Carotid pulsation may be very prominent (dancing carotid).

Blood pressure:

- Systolic arterial pressure is increased due to a large stroke volume, whereas the diastolic pressure is decreased due to regurgitation of blood from aorta to ventricle. Therefore pulse pressure is increased (difference between systolic and diastolic BP is more than 60 mm Hg). You will be surprised when the reading of diastolic blood pressure is zero.
- With the development of heart failure peripheral vasoconstriction may occur, arterial diastolic pressure may rise causing pulse pressure to become narrow and attenuation of peripheral signs of AR.

INVESTIGATIONS

X-ray chest

This shows left ventricular enlargement and dilatation of the ascending aorta.

ECG

- It shows features of left ventricular hypertrophy.
- Pattern of left ventricular diastolic overload may be present as prominent Q waves in I, aVL, V3-V6. T waves may be initially tall and upright in left precordial leads, they become inverted with ST depression later.

Echocardiography

Echocardiography is helpful in:

- Detection of aortic regurgitation.
- Assessment of cause
- Assessment of severity by measuring aortic regurgitant orifice size and the aortic regurgitant flow.
- Assessment of hemodynamic effects such as left ventricle size (left ventricular end-systolic and end-diastolic dimensions) and LV hypertrophy.

Cardiac catheterization and angiography

Doppler echocardiography can asses the severity of AR , therefore cardiac cathterization is not required in majority of cases. In catheterization, we can detect AR, its severity, assessment of aorta for

dilatation or dissection, structural abnormalities of aortic valve and hemodynamic effects of AR (left ventricular volumes and ejection fraction).
Now cardiac catheterization is performed to assess coronary arteries before surgery.

TREATMENT

ASYMPTOMATIC PATIENT

Mild to moderate AR

Patients who have mild to moderate AR and are asymptomatic who have normal or minimally increased cardiac size require no therapy. They should be followed with clinical evaluation yearly and echo 2-3 yearly. Antibiotic prophylaxis for endocarditis and monthly injection for prophylaxis of rheumatic fever is recommended. These patients should avoid competitive sports and heavy physical exercise.

Severe AR

Asymptomatic patient with severe AR and normal left ventricular function should be examined every 6 months.

Vasodilator therapy is given to patients with severe AR and normal left ventricular systolic function or dysfunction even they are asymptomatic. Vasodilators may be given to those patients who are awaiting surgery or they are not surgical candidate. Vasodilators such as ACE inhibitors, nifidipine, hydralazine can reduce the severity of regurgitation. Nitrates, digoxin and diuretic may also be used.
Beta blocker may slow the rate of aortic root dilatation in Marfan's syndrome.

Medical treatment

- Vasodilators: hydralazine, ACE inhibitors, nitrates.
- Diuretics, digoxin.
- Endocarditis prophylaxis.
- Rheumatic fever prophylaxis

SYMPTOMATIC PATIENT

- Aortic valve replacement (AVR) is the treatment of choice in sysmptomatic patients.
- Patients who are candidates for surgery but who have severe decompensated left ventricular dysfunction, vasodilator therapy may be particularly helpful in stabilizing patients while preparing for surgery. Digoxin and diuretics may be used in these patients.
- Vasodilator therapy, digoxin and diuretics are also effective for those patients who are considered to be inoperable due to comorbids.

MANAGEMENT OF MODERATE TO SEVERE AR

Asymptomatic patient

Asymptomatic patients with moderate to severe AR require long-term vasodilator therapy. When there is evidence of LV dysfunction (EF declines to the range of 50-55%), the LV end-systolic diameter rises to 55 mm or greater, or LV end-diastolic dimension rises to 75 mm or greater operation should be strongly considered even without symptoms.
Further LV dilatation or dysfunction may become irreversible and the cardiomegaly and LV dysfunction may persist after surgery, resulting in poor postoperative outcome.

Symptomatic patient

With normal left ventricular function
Patients with significant AR and normal left ventricular ejection fraction (EF> 50%) who have functional class II or III symptoms should undergo aortic valve replacement.

With abnormal left ventricular function
Symptomatic patients with mild to moderate LV dysfunction (EF 25-50%) should undergo aortic valve replacement (AVR).
Patients with severely depressed LV function EF < 25% or LV end- systolic dimension > 60 mm, are at high operative risk and not all patients benefit from valve replacement.

Indications of aortic valve replacement (AVR)

- Symptomatic patient with severe AR (NYHA class II or III).
- In asymptomatic patient surgery is advised if there is mild to moderate LV dysfunction (EF <50-55%) and severe left ventricular dilatation (end-systolic diameter >55 mm or end-diastolic diameter > 75 mm.

TRICUSID STENOSIS

ETIOLOGY

Rheumatic heart disease (most common). It is frequently associated with mitral or aortic valve disease. More common in women.

PATHOPHYSIOLOGY

Tricuspid valve stenosis results in a reduced cardiac output which is restored towards normal when the right atrial pressure increases. The resulting systemic venous congestion produces hepatomegaly, ascites and dependent edema.

CLINICAL FEATURES

Symptoms

- Symptoms of associated left-sided rheumatic valve lesion.
- Abdominal pain (due to hepatomegaly) and swelling (due to ascites) and peripheral edema.

On examination

1. *JVP*: giant "a" wave in JVP.
2. *Pulsating liver:* Deep palpation of liver may show presystolic pulsation.
3. *Murmur:* Mid-diastolic murmur at tricuspid area i.e. along lower left sternal border, loud on inspiration.

ECG

- This shows "P" pulmonale due to right atrial hypertrophy.

TREATMENT

- Diuretic therapy and salt restriction.
- Surgical replacement of tricuspid valve.

TRICUSPID REGURGITATION

ETIOLOGY

Organic tricuspid regurgitation

- Rheumatic heart disease
- Infective endocarditis particularly in IV drugs abusers.
- Carcinoid syndrome
- Ebstein's anomaly: Congenitally malposition of tricuspid valve.

Functional (when right ventricle dilates).

- Right ventricular dilatation due to chronic left heart failure.
- Corpulmonale.
- Right ventricular infarction
- Pulmonary hypertension.

CLINICAL FEATURES

Symptoms

Features of right heart failure.

Clinical Examination

- **JVP:** There is a large v waves. JVP elevated if right ventricular failure has occurred.
- Right ventricular heave.
- **Murmur:** On auscultation, there is a pansystolic murmur along the left parasternal border. Murmur increases during inspiration (that differentiates from pansystolic murmur of mitral regurgitation that increases on expiration).
- **Pulsatile liver:** Palpation of liver shows systolic pulsations.

INVESTIGATIONS

X-ray chest

Right atrial and ventricular dilatation.

Echocardiography

- Right ventricular dilatation.
- Abnormal tricuspid valve may be present.
- Estimation of pulmonary artery pressure from Doppler echocardiography.

TREATMENT

- *Functional tricuspid regurgitation:*
  Use of diuretics decrease pre-load and so improve the condition when tricuspid regurgitation is due to right ventricular dilatation.
  Mitral valve replacement, because it is the primary cause.
- *Organic tricuspid regurgitation:* Surgical repair or valvoplasty and very occasionally replacement of tricuspid valve.

PULMONARY STENOSIS (PS)

ETIOLOGY

- Congenital (most common)
- Rheumatic fever (rare)
- Carcinoid syndrome
- Aneurysm of sinus of Valsalva
- Fallot's tetralogy

CLINICAL FEATURES

Aduluts with isolated mild to moderate PS are usually asymptomatic. Patients with severe PS may present with exertional fatigue, dyspnea, lightheadedness, and chest discomfort (right ventricular angina). Cyanosis may be present when a patent foramen ovale (PFO) or ASD permits right to left shunt.

EXAMINATION

Palpation

It shows signs of right ventricular hypertrophy i.e. there is left parasternal heave.
Thrill in 2nd left intercostals space.

Auscultation

S1 is normal.
Single S2 with diminished P2

Murmur: On auscultation there is an ejection systolic murmur at the pulmonary area (2nd left intercostals space) radiating towards the left shoulder. There may be an ejection click before the murmur. Intensity of the murmur increases with inspiration.

JVP: JVP shows prominent "a" wave.

INVESTIGATION

- ECG: It shows right atrial and right ventricular hypertrophy.
- X-ray chest: There is post- stenotic dilatation of the pulmonary artery. Right atrial and right ventricular enlargement. Vascularity is reduced in severe PS producing oligemic lungs.
- Echocardiography: It demonstrates anatomical valvular abnormality and severity of PS. Right ventricular pressure is measured indirectly from tricuspid regurgitation gradient.

TREATMENT

Balloon valvuloplasty is recommended when the gradient across the right ventricular outflow tract is greater than 50 mmHg at rest (measured by echo or right heart catheterization) or when the patient is symptomatic.

PULMONARY REGURGITATION (PR)

ETIOLOGY

- This usually results from dilatation of valve ring secondary to pulmonary hypertension or dilatation of the pulmonary artery due to connective tissue diseases such as Marfan syndrome.
- Infective endocarditis.
- As a complication of surgery for PS or tetralogy of Fallot (TOF)
- Congenital malformations of pulmonic valve.
- Carcinoid syndrome
- Rheumatic fever
- Syphilis

Clinical features

- Patients of PR present with right heart failure.
- Examination reveals right ventricular heave, thrill may be present in pulmonary area
- An early diastolic murmur is usually heard at 3rd or 4th left intercostals space.
- Loud P2 in case of pulmonary hypertension.

Investigations

- *ECG*: Right ventricular hypertrophy
- *Chest X-ray:* enlarged right ventricle and pulmonary artery shadow.
- *Echo:* RV dilatation, RV hypertrophy, detection of PR and its severity.

Treatment

- Digoxin for right ventricular dilatation or failure.
- Treatment of underlying cause.
- Valve replacement (with bioprosthetic valve) if PR is severe due to surgery of tetralogy of Fallot.

CONGENITAL HEART DISEASE

A congenital cardiac malformation occurs in about 1% of live births. There is an overall male predominance, although some individual lesions such as atrial septal defect and patent ductus arteriosus occur more commonly in females.

ETIOLOGY

Exact cause unknown but following are the recognized associations.

1. Maternal rubella infection: causing persistent ductus arteriosus, pulmonary valvular and arteriolar stenosis.
2. Maternal alcohol abuse → septal defects
3. Maternal drug treatment and radiation
4. Genetic abnormalities
5. Chromosomal abnormalities: septal defects and mitral and tricuspid vale defects are associated with Down's syndrome. Coarctation of aorta is associated with Turner's syndrome.

COMMON CONGENITAL LESIONS

Congenital lesions	%	Occurrence in first - degree relatives (%)
VSD	39	4
ASD	10	2
PDA	10	4
Pulmonary stenosis	7	-
Coarctation of aorta	7	2
Aortic stenosis	6	4
Fallot's tetralogy	6	4
Others	15	-

COMMON SIGNS AND SYMPTOMS

1. **Central cyanosis**: Occurs due to right-to-left shunting of blood or because of complete mixing of systemic and pulmonary blood flow.
2. **Pulmonary hypertension:** Results from large left-to-right shunts. The persistently raised pulmonary flow leads to the development of increased pulmonary artery vascular resistance and consequent pulmonary hypertension.
3. **Clubbing of the fingers:** Associated with prolonged cyanosis.
4. **Paradoxical embolism:** A thrombus formed in systemic veins can enter the systemic arterial system when a communication exists between the right and left heart such as ASD, VSD.
5. **Reduced growth:** Growth retardation is common in children with cyanotic heart disease.
6. **Syncope:** is common when severe right or left ventricular outflow tract obstruction is present.

Common symptoms and signs

- Central cyanosis
- Pulmonary hypertension
- Clubbing of the fingers
- Paradoxical embolism
- Reduced growth
- Syncope

CONGENITAL HEART DISEASES

Cyanotic heart disease

- Tetralogy of Fallot (TOF)
- Transposition of great arteries (TGA)
- Tricuspid atresia
- Truncus arteriosus
- Eisenmenger's syndrome

Acyanotic heart disease

With left to right shunt

- ASD, VSD, PDA

With no shunt

- Coarctation of aorta
- Congenital aortic stenosis (bicuspid aortic valve).
- Pulmonary stenosis, tricuspid stenosis
- Dextrocardia
- Ebstein's anomaly.

VENTRICULAR SEPTAL DEFECT (VSD)

Ventricular septal defect is the most common congenital cardiac malformation. However in majority of cases it presents and is diagnosed in childhood. Most common congenital heart disease presenting in adult life is ASD.

TYPES

1. Muscular VSD
2. Membranous VSD, further divided into:
   - Supracristal
   - Perimembranous VSD
   - Malalignment VSD

PATHOPHYSIOLOGY

Left ventricular pressure is higher than right ventricular pressure; blood therefore moves from left to right and pulmonary flow increases resulting in pulmonary hypertension.

When pulmonary blood flow is very large, progressive changes take place in the pulmonary vessels causing pulmonary arterial pressure equal to the systemic pressure. Consequently shunt is gradually reduced or reversed (becoming right to left). This reversal of shunt is called **Eisenmenger's syndrome.** Now the patient develops central cyanosis and clubbing.

Larger defects may cause heart failure in the first 6 months of life and if the defect is not closed by age 2 years, irreversible pulmonary hypertension may develop. About 40% defects close spontaneously by the age 3.

Clinical features depend on the size of the defect. Most of the small defects are asymptomatic and close spontaneously, while the large defects present with heart failure during infancy, therefore it is uncommon that adults first time present with previously undiagnosed significant VSD. Affected individuals with uncorrected defects who survive to adulthood may present with small hemodynamically insignificant defects or larger defects with Eisenmenger's syndrome (right to left flow) developing cyanosis and clubbing.

CLINICAL FEATURES

Infants and children

- Patients with small defect are usually asymptomatic and referred by pediatrician due to presence of pansystolic murmur.
- Patients with large defects present with breathlessness, CCF and failure to thrive in 2nd or 3rd month of life.

Adults

- Adults with small defects are asymptomatic presenting with pansystolic murmur in the 3rd or 4th intercostals space along with the left sternal border.
- Patients with moderate defects often present with shortness of breath.
- Patients with large defect present with Eisenmenger syndrome, signs of pulmonary hypertension such as right ventricular heave, palpable and loud P2 and right-sided S4 and right heart failure.

On examination

Palpation

- Displaced apex beat.
- Palpable thrill along the left sternal border.
- Palpable P2

Auscultation

- Pansystolic (holosytolic) murmur is audible, maximal at the left sternal border in the left third or fourth intercostals space with radiation to the right parasternal region. Smaller defects produce louder murmur.
- Third heart sound and diastolic murmur at apex due to increased flow across the mitral valve may be present.
- High defects may be associated with aortic regurgitation (AR) due to prolapse of a valve leaflet.
- Signs of pulmonary hypertension and then tricuspid regurgitation may be present.

INVESTIGATIONS

X-ray chest

Small defects produces no abnormal x-ray findings. Larger defects show prominent pulmonary artery and cardiomegaly.

ECG

Normal or features of both left and right ventricular hypertrophy.

Echocardiography

The size and location can be assessed by echocardiography; main pulmonary artery dilatation may be seen. Doppler echocardiography is more informative.

Right heart catheterization

It permits the definitive diagnosis of defect and also measures pulmonary vascular resistance. The higher the right ventricular oxygen saturation, the greater is the degree of shunting.

MANAGEMENT

1. Small VSD (pulmonary to systemic flow ratio < 1.5) requires no specific treatment, only infective endocarditis prohylaxis should be advised.
2. Indications of surgery
   a. Surgery is recommended in significant VSD, if systemic to pulmonary shunt ratio (Qp/Qs) is >1.5/1.0. This ratio is calculated by the data obtained in cardiac catheterization.
   b. Pulmonary artery systolic pressure > 50 mmHg.
   c. Increased LV and LA size.
   d. Deteriorating LV function in the absence of irreversible pulmonary hypertension
   e. Perimembranous or outlet VSD with more than mild aortic regurgitation
   f. History of recurrent endocarditis
3. After development of pulmonary hypertension surgical mortality risk is about 50%.
4. Large defect requires surgical repair, but if the shunt is reversed (Eisenmenger's syndrome) surgery is contraindicated.
5. As large number of VSD close spontaneously, surgery can be delayed in infancy to late childhood if there is no heart failure or pulmonary hypertension.
6. Device closure: Now devices are available and some of the VSDs may be closed percutaneously during cardiac catheterization.

ATRIAL SEPTAL DEFECT (ASD)

ASD is the most common shunt lesion in adults. It often remains undetected until adulthood because patients are often asymtomatic. It is more common in women than in men.

TYPES

There are two types of ASD.

Ostium secundum ASD (75%)

Ostium secundum atrial sepatal defect is the most common type (70% of patients) and results from defect in the region of the fossa ovalis. In this type there is no involvement of AV valves.

Ostium primum ASD (15%)

Ostium primum atrial septal defect results from absence of septum primum (at the lower portion of the atrial septum. It is more common in Down's syndrome. In this type there is also involvement of AV valves.

Sinus venosus defect (10%)

Sinus venosus defect is in the upper part of the septum near the entrance of the inferior vena cava and coronary sinus (therefore producing communication between coronary sinus and left atrium.

PATHOPHYSIOLOGY

- Communication at the level of atria allows left-to right shunting of blood causing volume overload on right side of heart. Because the pulmonary vascular resistance is low and the right ventricle is easily distended (i.e. it is compliant), there is a considerable increase in right heart output. A large ASD (Qp/Qs > 2.0/1.0) may cause CCF and failure to thrive in infancy or childhood.
- An undetected significant shunt (Qp/Qs > 1.5/1.0) probably causes symptoms over time in adolescence or adulthood as following:
  Dyspnea on exertion develops in 30% of patients by the 3rd decade and in 75% of patients by the 5th decade.
  Supraventricular arrhythmias (atrial fibrillation or flutter) and right sided heart failure develop by the age 40 years.

Paradoxical embolism (from right to left) resulting in TIA or stroke can call the diagnosis to attention.

Pulmonary hypertension may develop at any age.

CLINICAL FEATURES

Symptoms

- Asymptomatic for many years, if there is small or moderate defect and no pulmonary hypertension. Normal or minimally diminished exercise tolerance may develop.
- Exertional dyspnea usually after age 30.
- Palpitations due to atrial arrhythmia
- Patients are more prone to develop recurrent pulmonary infections.
- Right ventricular failure with large defect and prolonged pulmonary hypertension may develop later in life.
- Presence of cyanosis indicates reversal of shunt (Eisenmenger's syndrome).

On CVS examination

Palpation

- Right ventricular heave.
- Palpable P2

Auscultation

- Loud P2, wide fixed splitting of second heart sound is the hallmark of ASD, although not always present.
- Murmur: Ejection systolic murmur best heard at 2nd left intercostals space. A mid-diastolic rumble produced by increased flow through tricuspid valve may be present at the lower sternal border.
- Murmur of MR also present in ostium primum defect.
- JVP shows *a* wave equal to *v* wave.

INVESTIGATIONS

X- ray chest

- Cardiomegaly due to right atrial and ventricular enlargement.
- Prominent pulmonary artery.
- Pulmonary plethora (plethora means fullness) due to increased pulmonary flow.
- Small aortic knuckle due to chronic low cardiac output state.

ECG:

- Sinus rhythm or AF.
- Right axis deviation.
- Negative P waves in inferior leads in sinus venosus- superior vena caval defects
- Complete right bundle branch block (RBBB).
- Tall R in V1 indicates pulmonary hypertension.

Echocardiography

Echocardiography is helpful in the following ways:

- It can identify the size and type of defect.
- It estimates pulmonary artery pressure.
- It demonstrates right ventricular hypertrophy.
- It detects direction of shunt.
- It demonstrates pulmonary arterial dilation.
- It also demonstrates paradoxical motion of the interventricular septum.
- Transesohageal echocardiography can detect small ASD that is missed on routine transhoracic 2-D echocardiography.

Cardiac catheterization

Cardiac catheterization is not performed unless the patient has large defect on echocardiography.

- It is the definitive diagnostic procedure.
- It quantifies the shunt.
- It measures pulmonary vascular resistance.

MANAGEMENT

After diagnosis of ASD (usually echo based) decision is to be made whether to close the defect or not. Following features help in making the decision:

Indications of intervention

1. Intervention is advised in asymptomatic children with
   - Significant ASDs (>5mm)
   - With Qp/Qs ratio > 1.5 or associated with right –sided heart dilatation
   - No sign of spontaneous closure.
2. Insignificant ASDs (Qp/Qs < 1.5) do not require closure.
3. In patients with pulmonary hypertension (pulmonary artery pressure > 2/3 systemic arterial blood pressure or pulmonary arteriolar resistance > 2/3 systemic arteriolar resistance) closure may be recommended if there is net

left to right shunt of at least 1.5:1, evidence of pulmonary artery reactivity when challenged with a pulmonary vasodilator such as oxygen during cardiac catheterization.

4. Intervention should not be performed in reversal of shunt (Eisenmenger's syndrome) because of risk of acute right heart failure.

Choice of intervention

Subcutaneous insertion of device

Closure of ASD secundum during cardiac catheterization is now increasing. In this technique an umbrella-like occlusion device is deployed from the venous approach.

Surgery

Surgery is performed in sinous venosus or ostium primum defects or with ostium secundum defect if anatomy is not suitable for device closure.

- Endocarditis is rare in ASD and prophylactic antibiotics are not required.

If surgically not corrected

- Patient with small shunt may live a normal life.
- Pulmonary artery hypertension is more common with primum defect.
- After age 40, pulmonary hypertension, cardiac arrhythmia, and heart failure may occur.
- Paradoxical embolism is a risk especially in case of pulmonary hypertension.
- Surgery may be performed after age 40 if shunt is left to right.

PATENT DUCTUS ARTERIOSUS (PDA)

PDA is most often diagnosed in childhood. This is more common in females and is sometimes associated with maternal rubella infection.

PATHOPHYSIOLOGY

During fetal life, before the lungs begin to function, most of the blood from the pulmonary artery passes through the ductus arteriosus into the aorta. Normally the ductus closes soon after birth, but sometimes it fails to close. As the pressure in aorta is higher than the pulmonary artery, there will be a continuous arteriovenous shunt. As much as 50% of the left ventricular output may be recirculated through the lungs. This leads to an increased pulmonary venous return to the left heart and an increased left ventricular volume overload.

Reversal of shunt

With the resulting rise in pulmonary vascular resistance, pulmonary artery pressure rises further until it equals or exceeds aortic pressure. The shunt through the defect may then reverse (Eisenmenger's syndrome) causing central cyanosis that is more marked in the feet and toes than in upper part of body.

Severity of PDA

Silent PDA: Tiny PDA detected nonclinically, usually on echo.

Small PDA: Continuous murmur and Qp/Qs < 1.5/1.0

Moderate PDA: Continuous murmur and Qp/Qs = 1.5 to 2.2/1.0

Large PDA: Qp/Qs >2.2/1.0

Eisenmenger: Continuous murmur absent, pulmonary hypertension.

CLINICAL FEATURES

Symptoms in children and adults

- Small shunt: No symptoms for the years.
- Moderate shunt: Dyspnea or palpitation due to from atrial arrhythmias.
- Large shunt: Growth retardation, symptoms of left heart failure or pulmonary hypertension. Left heart failure is due to volume overload on left side. Pulmonary hypertension leads to

Eisenmenger's syndrome with hopxemia and cyanosis more in feet than hands.

On Examination

Pulse:
Pulse is bounding (large volume) due to increased left heart blood flow and decompression of aorta into the pulmonary artery (wide pulse pressure).

Blood pressure
Wide pulse pressure, low diastolic blood pressure due to rapid decompression of aorta.

Auscultation

- Reversed splitting of second heart sound if the shunt is large.
- Murmur: Continuous machinery murmur (due to turbulent aortic to pulmonary arterial shunting in both systole and diastole), best heard at the first and second intercostals space at the left sternal border. With moderate degree of pulmonary hypertension the diastolic component of murmur disappears leaving a systolic murmur only.

INVESTIGATIONS

X-ray chest:

- Cardiomegaly with a prominent left atrium and ventricle.
- Increased pulmonary vascular marking.

ECG:

Left atrial & left ventricular hypertrophy.

Echocardiography

Dilated left atrium and left ventricle but imaging of the ductus in adults is usually difficult. Doppler echo is diagnostic. Pulmonary artery pressure may be determined.

Cardiac catheterization

Right heart catheterization is performed to confirm the diagnosis, to see the severity of left to right shunt, and whether the pulmonary artery hypertension and pulmonary vascular resistance are present

MANAGEMENT

Premature infant: Medical treatment is indomethacin, which inhibits prostaglandin production and stimulates duct closure.

Children and adults

Clinically detectable PDA either large or small should be ligated. In the presence of severe pulmonary hypertension, duct closure is not advised and it is contraindicated if the pulmonary hypertension becomes irreversible.

Methods of closure

Transcatheter closure
Transcatheter closure by insertion of coil (a device) for ducts smaller than 8 mm during cardiac catheterization is becoming preferable in uncomplicated PDA and it is the method of choice for ductal closure if appropriate resources and experienced staff are available. Endocarditis prophylaxis is given for 6 months following PDA device closure.

Surgery
Surgical closure of duct is advised in patients in whom the PDA is too large for device closure or at centers where device insertion facilities are not present.

COARCTATION OF AORTA

Coarctation is narrowing of aorta at or just distil to the region where ductus arteriosus joins the aorta i.e. most common lesion is below the origin of left subclavian artery. However narrowing may be proximal (pre- ductal).

In 80% of cases coarctation of aorta is associated with a *bicuspid aortic valve.* It is 2-5 times more common in *males.* Severe narrowing of the aorta leads to elevation of blood pressure proximal to the narrowing and low blood pressure below the narrowing that encourages the formation of a collateral arterial circulation involving the periscapular and intercostals arteries. Decreased renal perfusion can lead to development of systemic hypertension.

Associations

Coarctation of aorta is more common in males. It is also associated with bicuspid aortic valve, VSD, congenital mitral valve stenosis or regurgitation, aneurysms of circle of Willis and Turner's syndrome.

CLINICAL FEATURES

Neonates

Rapid, severe obstruction in infancy is an important cause of heart failure in the newborn due to sudden increase in left ventricular wall stress after closure of the arterial duct.

Infants and children

Most infants and children are asymptomatic, with finding of weak femoral pulses and hypertension being detected during routine medical care. Complaints of headache, cold extremities, and claudication with exercise may be noted in older childern and adolescents. A midsystolic murmur over the anterior chest, back and spinous processes may be heard.

Adults

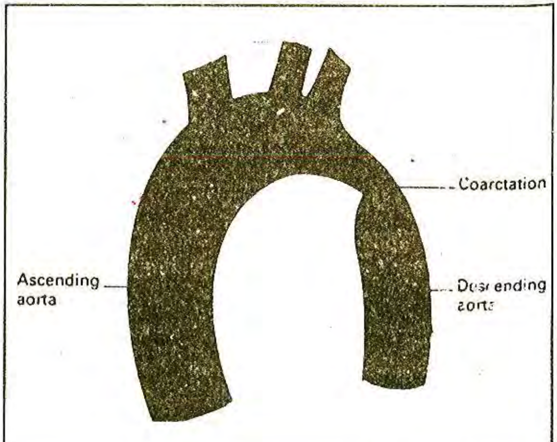
- Adults may be asymptomatic or may present with minimal symptoms of headache, epistaxis, leg weakness on exertion or some serious symptoms of left ventricular failure, angina, aortic stenosis, aortic dissection or cerebral hemorrhage.
- Coarctation is said to be significant if the gradient across the coarctation site is >20 mmHg at angiography with or without proximal systemic hypertension.
- On examination, patient has upper limb systemic hypertension. There is at least 10 mm Hg higher blood pressure in the upper limb than in the lower limb (brachial pressure > popliteal pressure). There is radiofemoral delay. Auscultation reveals interscapular systolic murmur. Fundoscpic examination can reveal " corkscrew" tortuosity of retinal arterioles.

Complications of coarctation of aorta

- Aortic rupture
- Dissection of proximal thoracic aorta or an aneurysm distal to the coarctation.
- Infective endocarditis on bicuspid aortic valve or on coarctation site.
- Intracerebral hemorrhage due to rupture of aneurysm of the circle of Willis.

On Examination

1. The upper body may be better developed than the lower.
2. Blood pressure: Systolic blood pressure is raised in upper limbs (especially right arm) but normal or low in lower limbs while the diastolic blood pressure is similar.
3. Femoral pulses are weak, and simultaneously palpafion of brachial and femoral pulses reveals delayed arrival of femoral pulse (radiofemoral delay).
4. Late systolic murmur over coarctation can be heard at base, better on back between scapulae especially over the spinous processes.
5. There may be an associated aortic regurgitation due to bicuspid aortic valve causing ejection systolic murmur in aortic area.
6. Collateral circulation may be detected in the older children & adults in the form of visible arteries around the scapula and below the ribs posteriorly.



INVESTIGATION

X-ray chest:

- Dilated aorta indented at the site of the coarctation manifested in the upper right mediastinum, shaped like a figure "3" due to pre and post stenotic dilatation.
- Rib notching: in adults tortuous & dilated collateral intercostals arteries may erode the undersurface of the ribs called rib notching.

ECG

Shows left ventricular hypertrophy.

MRI

MRI is also a useful diagnostic technique usually performed before and after intervention.

Cardiac catheterization

Aortography is necessary only when the diagnosis is not adequately confirmed clinically or non- invasively such as on echocardiography.

TREATMENT

Surgery

Surgical excision of the coarctation and end-to-end anastomosis of the aorta is the surgical procedure of choice. When surgery is performed in childhood, hypertension usually subsides completely, however if operation is performed in adulthood, hypertension persists in 70% of cases because of previous renal damage due to hypertension. Surgery becomes difficult if performed after the age of 15, therefore should be resected early, however surgery may be performed under age 40 years if patient has refractory hypertension or significant LV hypertrophy.

Balloon angioplasty

Balloon dilatation with or without stenting is also successful, but aortic tear may be the complication.

TETRALOGY OF FALLOT (TOF)

It is the most common cause of congenital cyanotic heart disease and a common cause of visit to emergency of pediatric cardiology. Without surgical intervention most patients die in childhood.

It comprises of following 4 defects.

1. Membranous VSD
2. Pulmonary stenosis usually at subvalvular level (right ventricular outflow obstruction).
3. Dextro-positioning of aorta (overriding of aorta)
4. Right ventricular hypertrophy.

Associated anomalies

- ASD (tetralogy plus ASD is called pentalogy of Fallot).
- Right sided aortic arch (in 25%).
- Abnormal course of coronary arteries (in 5%).
- Absent pulmonary valve syndrome

CLINICAL FEATURES

Children are usually cyanosed but cyanosis may not be present in neonates because it is only when right ventricular pressure rises equal to or exceeds left ventricular pressure producing right to left shunt.

Tetralogy spell

The affected child suddenly becomes cyanosed, often after feeding or a crying attack, and may become apnoeic and unconscious. These attacks are called tetralogy spells. Cause of spell may be increased right ventricular outflow obstruction or reduced systemic vascular resistance.

Degree of cyanosis depends on the following 2 factors:

1. Severity of right ventricular outflow obstruction: Higher the obstruction, greater is the cyanosis.
2. Level of systemic vascular resistance: Lower is the systemic resistance, greater is the cyanosis.

Fever and dehydration reduce systemic vascular resistance, causing more shunting of blood from right to left side resulting in acute fall in arterial oxygen saturation called Fallot's spell. Patient presents with shortness of breath and cyanosis.

In order children Fallot's spells are uncommon, but cyanosis is frequent. Growth retardation, digital clubbing and polycythemia are also seen. Without surgical correction most patients die during infancy or childhood.

On examination

- Cyanosis.
- Clubbing
- Right ventricular heave
- Systolic thrill along the left sternal border
- Early ejection systolic murmur that is aortic in origin (as most of the blood flows through the aorta because of severe pulmonary stenosis). This murmur may be heard at the left lower sternal border and apex.
- Remember that the murmur in TOF is the murmur of pulmonary stenosis not the murmur of VSD because pressure is equal on both sides of VSD (no gradient, no murmur).With extreme pulmonary outflow tract obstruction (pulmonary stenosis) and during spell, no murmur may be detected because little blood can pass through pulmonary valve (in patient without spell blood flow across the stenotic pulmonary valve creates murmur).

INVESTIGATIONS

ECG.

This shows right atrial and ventricular hypertrophy

X-ray chest

It shows a large right ventricle and small pulmonary artery (described as "**boot-shaped**" heart).

Echocardiography

It shows:

- Discontinuity between the aorta and the anterior wall of ventricular septum.
- Aortic root is enlarged and overrides VSD
- Severe right ventricular hypertrophy
- Malformed thickened pulmonary valve.
- Perimembranous VSD with right to left shunt.
- Aortic regurgitation may be present.

Cardiac catheterization

It reveals:

- Gradient across the pulmonary outflow tract.
- Normal pulmonary artery pressure.
- Equalization of RV and LV pressure.

TREATMENT

Total Correction (TC)

The definitive management is total correction of defect by surgical correction of pulmonary stenosis and closure of ventricular septal defect and can be performed even in infancy. Primary surgical correction may be undertaken prior to age 5, prognosis after operation is good.

Blalock shunt

If pulmonary arteries are excessively small, early definitive repair is not possible and a temporary palliative procedure designed to increase pulmonary blood flow and to decrease hypoxia is performed. This consists of creation of shunt from a systemic to pulmonary artery (SP shunt) by anastomosis between subclavian artery to the side of pulmonary artery, this is called Blalock shunt. It gives relief for several years; however total correction is the ultimate goal. Pulse is not palpable on ipsilateral side after procedure.

Medical management

- Avoid vasodilators, they increase right to left shunt.
- Fallot's spells may need treatment with morphine, beta- blocker such as propranolol (Inderal), sodium bicarbonate, rehydration, oxygen and squatting position. (This position increases systemic vascular resistance).
- Antibiotic prophylaxis for endocarditis.

Personal experience

Young doctors working in adult cardiology emergency usually do not recognize cause of shortness of breath in patients of TOF with spell and give diuretic considering it as a symptom of heart failure. As the dehydration is usually the cause of spell, diuretics worsen the condition; contrary to this infusion of normal saline improves shortness of breath (without permission from senior, do not give diuretics to patient with cyanotic heart disease)

TRANSPOSITION OF GREAT ARTERIES

This is the malformation in which aorta originates from morphological right ventricle while pulmonary artery from morphological left ventricle.

There are mainly two types of transposition:

- Complete transposition or *D*-TGA
- Congenitally corrected transposition or *L* - TGA

COMPLETE TRANSPOSITION OR *D*-TGA

This is a common and potentially lethal form of heart disease in newborns and infants. It consists of origin of aorta from morphological right ventricle and pulmonary artery from morphological left ventricle. Systemic venous blood passes to the right atrium → right ventricle → aorta, while on other side pulmonary venous blood passes to left atrium → left ventricle → pulmonary artery. Therefore oxygenated blood circulates in one circuit and unoxygenated blood in other circuit. This system is not compatible with life unless mixing of the two circuits occurs through ASD, VSD or PDA. Diagnosis is made on echocardiography.

Clinical features

Dyspnea and cyanosis from birth, progressive hypoxemia and CCF.

Management

- Dilatation of duct (PDA) by prostaglandin E1 in the early neonatal period improves the arterial saturation by enhancing mixing.
- Balloon atrial septostomy: A catheter is passed from femoral vein to right atrium and puncture is performed with needle in interatrial septum that increases mixing of blood. This procedure is often life saving.
- Corrective surgery is performed later in life such as atrial switch operation or arterial switch operation.

CONGENITALLY CORRECTED TGA (L-TGA)

In this condition, ventricles are also on opposite side along with abnormal position of aorta and pulmonary artery (while in complete TGA only aorta and pulmonary artery originate from opposite side).

- Deoxygenated systemic venous blood passes from the right atrium through a mitral valve to a left ventricle and then into the pulmonary artery. Oxygenated pulmonary venous blood passes from the left atrium through tricuspid valve to right ventricle and then to aorta. The circulation is thus physiologically corrected, but the morphologically right ventricle supports the systemic circulation.
- Associated anomalies occur in 95% of patients such as VSD, pulmonary or subpulmonary stenosis, Ebstein-type anomalies of tricuspid valve.

Clinical features

- Patients without associated VSD are asymptomatic until late adulthood. Dyspnea due to CCF and palpitation due to supraventricular arrhythmias most often arise in 5th or 6th decade.
- Patients with VSD and pulmonary stenosis can present with paradoxical emboli or cyanosis, especially if pulmonary stenosis is severe.

Management

- Tricuspid valve replacement if there is moderate to severe TR (due to Ebstein- like anomaly in which downward displacement of tricuspid valve into the right ventricle resulting in tricuspid regurgitation).
- When TR is associated with poor right ventricle function then double-switch procedure is appropriate.

PULMONARY HYPERTENSION

Pulmonary arterial pressure more than the upper limit of normal i.e. 25 mm Hg systolic, 10 mm Hg end-diastolic or 15 mm Hg mean is called pulmonary hypertension. In pulmonary hypertension there is enlarged proximal pulmonary arteries, right ventricular hypertrophy and right atrial dilatation.

ETIOLOGY

Primary pulmonary hypertension (PPH)

Primary pulmonary hypertension is defined as pulmonary hypertension in the absence of other disease of lungs or heart. It develops mostly in young and middle aged women and is characterized by progressive right heart failure, leading to death in 2-8 years. Low cardiac output manifests as weakness and fatigue, systemic congestion presents as edema and ascites. Peripheral cyanosis develops due to systemic vasoconstriction as a result of low cardiac output. Syncope on exertion may also occur due to fixed cardiac output.

Secondary pulmonary hypertension

Hypoxia of any cause is the most important and potent stimulus of pulmonary arterial vasoconstriction leading to pulmonary hypertension.

Chronic lung disease

- Chronic bronchitis
- Emphysema
- Lung fibrosis

Increased pulmonary blood flow

- Left or right shunt through ASD, VSD, PDA.

Increased pulmonary venous pressure

- Mitral stenosis
- Left ventricular failure
- Mitral regurgitation
- Pulmonary thromboembolic disease.

CLINICAL FEATURES

- Pulmonary hypertension leads to dyspnea initially on exertion and later also at rest.
- Dull, reterosternal chest pain resembling angina may be present (likely to be due to reduced coronary blood flow to a markedly hypertrophied right ventricle).
- Syncope or near syncope: due to fixed cardiac output.

On examination

Inspection:

Prominent a wave in JVP

Cyanosis in late stages due to systemic vasoconstriction as a result of markedly reduced cardiac output.

Palpation

- Left parasternal heave due to right ventricular hypertrophy.
- Systolic pulsation in second left intercosatal space due to dilated pulmonary artery.

Auscultation

- Loud pulmonary competent of 2nd heart sound (P2).
- Systolic ejection click and flow murmur in pulmonary area.
- Right ventricular S4.
- In advanced cases, tricuspid and pulmonary regurgitation and signs of right heart failure (Cor pulmonale) are found.

INVESTIGATION

ECG

Right ventricular and often right atrial hypertrophy.

X-ray chest

- Enlargement of pulmonary artery and its main branches. Enlarged proximal pulmonary arteries taper rapidly not reaching to the periphery.
- Right ventricular enlargement and right atrial dilatation.

Echocardiography

- Echo usually demonstrates right atrial and right ventricular enlargement and thickened interventricular septum.
- Abnormal septal motion due to right ventricular pressure overload.
- It is helpful in evaluation of suspected mitral stenosis, pulmonary valvular disease;

Cardiac catheterization

Right heart catheterization is required for confirming the diagnosis and assessment of severity of pulmonary hypertension. It also allows

the exclusion of other causes such as intracardiac small shunt or thromboembolic disease.

Pulmonary function tests (PFTs)

PFTS may show reduced vital capacity.

MANAGEMENT

SECONDARY PULMONARY HYPERTENSION

- **Treatment of the cause.**
- **Supplemental oxygen** for at least 15 hours per day has been demonstrated to slow the progression of pulmonary hypertension in patients with COPD.
- **Inhaled nitric oxide** is effective in lowering the pulmonary artery pressure in critically ill patients with pulmonary hypertension.
- **Anticoagulation** advised in pulmonary hypertension of unknown cause since multiple small pulmonary emboli may produce this picture and they may get benefit.

PRIMARY PULMONARY HYPERTENSION (PPH)

There is no satisfactory treatment of primary pulmonary hypertension. Prognosis is poor. Supportive measures are following:

1. **Lifestyle changes:** It includes graded exercises like bike riding or swimming. Weight lifting and climbing upstairs (isometric activities) should be avoided because they can lead to syncope.
2. **Pregnancy should not be allowed** as it may worsen the disease leading to mortality of mother and /or child.
3. **Digoxin** is effective in patients with right ventricular failure from pulmonary hypertension.
4. **Diuretics:** patients with advanced PPH can have increased left ventricular filling pressure that contributes to the symptoms of dyspnea and orthopnea; therefore diuretics improve dyspnea. Diuretics are also first choice for right ventricular failure.
5. **Oxygen supplementation** if patient is hypoxemic at rest.
6. **Inhaled nitric oxide** may be helpful.
7. **Anticoagulants**: Significant survival benefit is seen with warfarin maintaining INR 2-3.
8. **Vasodilator therapy:** Chronic vasodilator therapy decreases pulmonary hypertension.
    - Calcium channel blockers such as nifidipine, diltiazem in high doses may produce dramatic reduction in pulmonary artery pressure.
    - Prostacyclin: Continuous intravenous infusion of epoprostenol (prostacyclin) has been shown to improve quality of life, exercise tolerance and survival. It is administered through central venous catheter that is surgically implanted and delivered by an ambulatory infusion system. *Side effects* of prostacyclin are flushing, headache, nausea, diarrhea and jaw discomfort that occurs with eating.
    - Phosphodiestrase inhibitors: Sildenafil (Viagra) is a potent pulmonary vasodilators
9. **Atrial septostomy:** Atrial septostomy allows right to left shunt and improves symptoms in patients with right heart failure or syncope due to limited cardiac output not responding to maximal medical treatment.
10. **Heart-lung or lung transplantation** two-year survival rate is 50%.

COR PULMONALE

Cor pulmonale is defined as right heart ventricular hypertrophy and dilatation secondary to pulmonary hypertension caused by diseases of the lung parenchyma and /or pulmonary vessels, unrelated to the left side of the heart.

Causes

- COPD (most common)
- Pneumoconiosis
- Pulmonary fibrosis
- Kyphoscoliosis
- Primary pulmonary hypertension
- Repeated attacks of subclinical or clinical pulmonary embolism.
- Lymphangitic infiltration from metastatic carcinoma.

Clinical features

- Features of primary disease such as dyspnea, cyanosis, clubbing and weakness.
- Features of right heart failure such as raised JVP, right ventricular heave. Murmurs of pulmonary and tricuspid regurgitation may be present.

Investigations

X-ray chest

Right ventricular enlargement and right atrial dilatation. Prominent pulmonary artery.

ECG

It shows right ventricular hypertrophy (right axis deviation, prominent R wave in VI and deep S wave in V6), right atrial abnormality (tall peaked P wave in lead II-called P pulmonale).

Echocardiography and Doppler studies

They demonstrate right ventricular dilatation and cause of pulmonary hyeprtension such as intracardiac shunt.

Treatment

- Treatment of the cause.
- *Diuretics*: They are used for right heart failure but should be in small doses because excessive fluid depletion may result in reduced output from the impaired right ventriclular filling.
- *Oxygen:* If required. Long-term oxygen therapy in COPD improves symptoms and prognosis.
- *Digoxin* is effective in patients with right ventricular failure from pulmonary hypertension.
- ACE inhibitors have no role in the management of right heart failure.
- Heart and lung transplantation is recommended for young patient.

ACUTE MYOCARDITIS

Acute myocarditis causes focal or diffuse inflammation of the myocardium. Majority of cases are due to infection caused by viral (most common), bacterial, rickettsial, fungal, or parasitic agents; but toxins, drugs and immunologic disorders can also cause myocarditis.

CAUSES OF MYOCARDITIS

Primary myocarditis

Myocarditis caused by acute viral infection is called primary myocarditis.

Viruses: Coaxsackie A and B, adenovirus, influenza virus, HIV virus, Epstein-Barr virus, herpes virus, cytomegalovirus, mumps virus, respiratory syncytial virus and rubella virus.

Secondary myocarditis

Myocarditis caused by non-viral cause is called secondary myocarditis

Infections

Bacterial: Diphtheria, brucellosis, H.influenza, mycoplasma, pneumococci, salmonella, streptococcus, staphylococcus

Protozoal; Entamoeba, trypanosomiasis

Fungal: Candida, actinomyces, aspergillus

Endocrine and metabolic disorders

Diabetes, hypo and hyperthyroidism, acromegaly, carcinoid syndrome, inherited storage diseases.

Connective tissue diseases

Scleroderma, SLE, polyarteritis nodosa

Infiltrative disorders

Hemchromatosis, hemosiderosis, sarcoidosis, amyloidosis.

Endomyocardial fibrosis and eosinophilic heart disease.

Toxins

Drugs: Doxorubicin, emetine, phenothiazines, lithium, chloroquine, dysopiramide.

Alcohol, irradiation

Neuromuscular disorders

Dystrophia myotonica, Friedreich's ataxia

CLINICAL FEATURES

- The clinical presentation of infectious myocarditis is variable.
- Many patients are asymptomatic and will have a complete resolution of myocarditis without complications.
- Patients may present with heart failure several days to a few weeks after the onset of an acute febrile illness or a respiratory infection; or heart failure without antecedent symptoms.
- Pleural chest pain secondary to pericarditis is common.
- Patient may present with life threatening arrhythmias or embolic events.
- Patient may present after months or years of development of dilated cardiomyopathy.

On examination

- Tachycardia.
- Pericardial friction rub may be heard.
- Features of congestive cardiac failure.
- S3 gallop, murmurs of tricuspid and mitral regurgitation may be present (due to dilatation of chambers).

INVESTIGATIONS

ECG

Non-specific ST segment and T wave abnormalities, arrhythmias or conduction delay.

X-ray

X-ray shows normal heart size initially and then cardiomegaly.

Cardiac enzymes

Cardiac enzymes may be elevated if the patient presents acutely usually within one month of symptoms.

Echocardiography

Transthoracic echocardiography is useful to assess the size of chambers and their function. In fulminant myocarditis there is increased ventricular wall thickness due to inflammation associated with interstitial edema.

MRI

MRI has sensitivity of 100% while specificity 90-100% in the diagnosis of acute myocarditis.

Endomyocardial biopsy

It is the gold standard for diagnosing myocarditis and is useful when a treatable cause is found.

Clinical pathological types of myocarditis

- Fulminant myocarditis
- Subacute myocarditis
- Chronic active myocarditis
- Chronic persistent myocarditis

TREATMENT

- Bed rest or limited activity as exertion increases viral replication.
- Standard heart failure therapy (diuretics, ACE inhibitors), and suppression of arrhythmia with beta- blockers. As vascular spasm is a component of myocarditis, agents that precipitate or exacerbate vascular spasm should be avoided; this may include the use of digoxin. Support with pressors such as dopamine and dobutamine and intraaortic balloon counterpulsation may be required.
- Immunosuppressive therapy with intravenous immunoglobulin or corticosteroid proved no significant benefit and is not advised.
- Treatment of the cause if identified.

Prognosis

Many cases of viral myocarditis resolve spontaneously, but in others cardiac function deteriorates progressively and may lead to dilated cardiomyopathy

CARDIOMYOPATHY

The cardiomyopathy is a general term indicating disease of the cardiac muscle primarily, not associated with the major causes of cardiac disease such as ischemic heart disease, hypertension, pericardial disease, valvular heart disease, or congenital defects. While some have specific causes, many cases are idiopathic.

TYPES

There are three types of cardiomyopathy according to their clinical presentation as following:

- Dilated cardiomyopathy (ventricular dilatation)
- Hypertrophic cardiomyopathy (myocardial hypertrophy)
- Restrictive cardiomyopathy (impaired ventricular filling).

DILATED CARDIOMYOPATHY

Dilated cardiomyopathy is characterized by dilatation and impaired ventricular contraction (LV dysfunction) leading to progressive left-sided and later, right-sided failure. Functional mitral and/or tricuspid regurgitation may occur. Arrythmias are common. Cause cannot be identified in most of the patients; myocarditis and chronic alcohol abuse are probably frequent causes of dilated cardiomyopathy.

Possible causes of dilated cardiomyopathy:

- Idiopathic (most common).
- Alcohol
- Viral myocarditis
- Familial and genetic factors
- Peripartum cardiomyopathy
- Diabetes mellitus
- Sarcoidosis
- Hemochromatosis
- Connective tissue disease such as multiple sclerosis

Clinical features

- Features of cardiac failure, arrhythmias or emboli.
- Cardiac failure, S3 gallop rhythm.
- Ventricular dilatation leads to functional mitral or tricuspid valvular regurgitation.

Investigations

- **X-ray chest** shows large flask-shaped heart (massive cardiomegaly).
- **Echocardiography** reveals dilatation of left ventricle, dilatation of right ventricle with poor global contraction. It helps in assessment of degree of left ventricular function, and exclusion of concomitant valvular or pericardial disease.
- **ECG:** shows tachycardia, conduction abnormalities, ST-segment and T wave changes, ventricular ectopics.
- **Cardiac biopsy** shows fibrosis and non-specific leukocyte infiltration.
- **Cardiac catheterization** shows left ventricular dilatation and dysfunction, high end-diastolic pressure, low cardiac output.

Treatment

- Management of cardiac failure and arrhythmia
- Prolonged bed rest and avoidance of alcohol in special cases.
- Prophylactic anticoagulation because arterial and pulmonary emboli are more common in dilated cardiomyopathy.

HYPERTROPHIC CARDIOMYOPATHY

- Hypertrophic cardiomyopathy is characterized by marked hypertrophy of the left and/or right ventricle particularly the interventricular septum in the absence of a cardiac or systemic cause (asymmetrical septal hypertrophy).
- The hypertrophied septum and the anterior movement of mitral valve across the outflow tract making contact with the ventricular septum in midsystole result in mechanical obstruction to left ventricular ejection. Some degree of mitral regurgitation may develop. The left ventricular outflow tract is narrowed during systole between the bulging septum and systolic anterior motion (SAM) of the anterior mitral leaflet causing obstruction to left ventricular emptying therefore called obstructive cardiomyopathy. The obstruction is worsened by factors that increase myocardial contractility (sympathetic stimulations, digoxin) or that decrease left ventricular filling (Valsalva's maneuver, peripheral vasodilators).
- In about 50% cases it is an <u>inherited as autosomal dominant trait,</u> some patients have

prolonged history of hypertension and some cases are sporadic. It is the most common genetically transmitted cardiac disorder. Incidence is 1 in 500 of the general population.

- This type of hypertrophy usually manifests in adolescents and young adults, most of the patients are identified during screening of relatives of patients with hypertrophic cardiomyopathy. It may manifest in 4^{th} or 5^{th} decade and sometimes in elderly.
- The physiological characteristic of HOCM is diastolic dysfunction (while systolic dysfunction in dilated cardiomyopathy) resulting in abnormal stiffness of left ventricle with resultant impaired ventricular filling. Left ventricular end-diastolic pressure increases resulting in pulmonary congestion and dyspnea.

Associations: Noonan syndrome, Friedreich's ataxia, Glycogen storage disease and Mitochondrial myopathies.

CLINICAL FEATURES

Symptoms

- Patient may be asymptomatic, diagnosed on echo during screening.
- *Dyspnea:* It is due to pulmonary congestion resulting from elevations in pulmonary venous and left atrial pressure because of stiffness of hypertrophic ventricles (diastolic dysfunction).
- *Chest pain:* This occurs on exertion or at rest due to compression of intramyocardial coronary arteries and increased oxygen requirement due to increased myocardial contraction and muscle mass. Chest pain usually does not respond to sublingual nitroglycerine.
- *Syncope:* Especially post-exertional due to inadequate cardiac output with exertion or from cardiac arrhythmia.
- *Palpitation:* It is due to arrhythmias. Atrial fibrillation is common and a poor prognostic sign. Ventricular arrhythmias are also common and sudden death may occur.
- *Sudden death:* This can occur at any age but the highest rates occur in adolescents and young adults.
- *Congestive heart failure*

On CVS Examination

Palpation:
Apex beat is displaced laterally, forceful and diffuse. A double apical pulsation (forceful atrial contraction produces a palpable fourth heart sound).

Auscultation:

- S1 is normal, often preceded by S4, normal S2.
- Late systolic murmur beast heard between the apex and left sternal border radiating to lower sternal border, axilla and base of heart but not into the neck vessel (that differentiates it from murmur of aortic stenosis). It is produced due to left ventricular outflow obstruction in late systole. This murmur is increased by Valsalva maneuver and by standing while decreased by squatting.
- A pansystolic murmur at apex may be heard due to mitral regurgitation as a result of systolic anterior motion of anterior leaflet of mitral valve).
- Reversed splitting of second heart sound.
- A fourth heart sound.

Pulse: A jerky carotid pulse with sharp upstroke (because of rapid ejection and sudden obstruction to left ventricular outflow during systole).

JVP: prominent *a* wave due to forceful atrial contraction.

INVESTIGATIONS

X-ray chest:
Heart usually not greatly enlarged

ECG:

- ECG demonstrates left ventricular hypertrophy
- Large abnormal Q waves in 20-50% of patients in leads II, III, aVF or V2-V6. (pseudo-infarction), left axis deviation.
- Occasionally LBBB or RBBB, APCs, PVCs, short PR may be present.

Echocardiography: It is diagnostic showing:

- Asymmetric left ventricular hypertrophy.
- Systolic anterior motion (SAM) of anterior leaflet of mitral valve.
- Small left ventricular cavity size.
- Dilated left atrium.
- Left ventricular diastolic dysfunction.

Cardiac catheterization

- Small hypercontractile left ventricle
- Dynamic left ventricular outflow obstruction
- Diastolic dysfunction.

ASSESSMENT

Patients should have risk stratification that includes history and physical examination, echocardiography, 24-48 hour Holter monitoring and ETT.

Poor prognostic factors (↑Risk of sudden death)

- Prior cardiac arrest or sustained VT
- Multiple or repetitive episodes of non-sustained VT
- Young age at diagnosis (<30 years)
- Extreme left ventricular hypertrophy and wall thickness of equal or greater than 30 mm on echo.
- Family history of HOCM with sudden death
- History of syncope
- Myocardial ischemia on thallium scan
- Abnormal blood pressure response (low BP) to ETT.
- LV outflow tract obstruction (outflow tract gradient >30 mm Hg

MANAGEMENT

- No specific treatment.
- Strenuous exercise should not be allowed.
- **Beta-blockers** help in relieving syncope, dyspnea and anginal pain. Calcium channel blocker especially verapamil, is also effective in symptomatic patient. If beta-blockers are not effective alone in reducing outflow obstruction calcium channel blockers or disopyramide may be combined with beta-blockers. Atrial fibrillation (AF) if develops, it worsens the symptoms. AF should be converted pharmacologically (with amiodarone) or electrically. All patients with AF should receive anticoagulants.
- **Diuretics:** Cautious use of diuretics may help reduce symptoms of pulmonary congestion.
- *Vasodilators and digoxin* should be avoided because they may aggravate left ventricular outflow obstruction.
- Dual chamber **pacemaker** insertion is advised in patients with severe symptoms and significant outflow obstruction especially in elderly patients.
- **Alcohol septal ablation:** Injection of alcohol into the septal branch of the left coronary artery (during cardiac catheterization) intentionally causes infarction of portion of interventricular septum that results in reduction of outflow obstruction, improvement of ventricular relaxation, regression of hypertrophy and reduction in symptoms. Main complication of the procedure is heart block requiring permanent pacemaker insertion.
- **Surgical treatment:** Surgical options are used when there is severe outflow obstruction in severe symptomatic patients not responding to medical treatment.
  - Myotomy-myectomy: Incising and resecting about 5 gm of hypertrophied septum using transaortic approach, often relieves obstruction as well as improving mitral regurgitation. Main complication of surgery is development of aortic regurgitation.
  - Mitral valve replacement: It abolishes obstruction by preventing systolic anterior motion of the mitral valve.

SUMMARY OF MANAGEMENT OF HYPERTROPHIC CARDIOMYOPATHY

1. Patients without outflow gradient (called hypertrophic non-obstructive cardiomyopathy)
   - Beta blocker, verapamil or diltiazem.
2. Patients with outflow gradient (called hypertrophic obstructive cardiomyopathy or HOCM)
   - Beta blocker plus disopyramide
3. Symptomatic patients with outflow gradient (HOCM) not responding to medical treatment:
   - Dual chamber pacemaker, septal ablation, myotomy-myectomy or mitral valve replacement.

RESTRICTIVE CARDIOMYOPATHY

Restrictive cardiomyopathy is characterized by impaired diastolic ventricular filling due to stiffness of ventricles with preserved systolic contractile function. Because of the abnormally elevated right atrial and ventricular filling pressures, cardiac filling is diminished. As a result, the clinical manifestations of restrictive cardiomyopathy usually are predominantly right-sided. There is high atrial pressure with atrial hypertrophy, dilatation and later atrial fibrillation.

Causes of restrictive cardiomyopathy

Amyloidosis, sarcoidosis, hemochromatosis radiation, carcinoid syndrome, scleroderma, myocardial fibrosis after open-heart surgery, Loffler's syndrome

Symptoms

1. Dyspnea and fatigue (due to low cardiac output).
2. Abdominal discomfort (due to hepatic congestion).
3. Restriction to ventricular filling results in persistently elevated venous pressures and consequent hepatic enlargement, ascites and dependent edema (right sided failure).

Signs

Physical signs are similar to those of constrictive pericarditis e.g.

- Raised JVP with diastolic collapse (Friendreich's sign) and raised JVP on inspiration (Kussmaul's sign).
- Cardiac enlargement with a third or fourth heart sound is common.

Investigations

- *Chest X-rays:* It shows mild to moderate cardiomegaly.
- *ECG:* Usually has low-voltage, conduction abnormalities, ST segment and T wave abnormalities.
- *Echocardiography:* It shows symmetrical myocardial thickening, usually a normal systolic function, but impaired ventricular filling.
- *Cardiac catheterization:* It shows higher diastolic pressure. Right and left ventricular pressure tracings demonstrate a characteristic "square root sign"—a deep and rapid early decline at the onset of diastole followed by a rapid rise to a plateau.
  Normal or mildly reduced left ventricular function.
  Cardiac catheterization helps in distinction from constrictive pericarditis.
- *Endomyocardial biopsy*: helpful in diagnosis.

Management

No treatment, diuretics may give some relief.

PERICARDIAL DISEASES

ETIOLOGY OF PERICARDITIS

Common

- Post- myocardial infarction
- Viral (e.g. coxsackie B, but often not identified).
- Tuberculosis.

Less common

- Uremia
- Malignant disease
- Trauma (e.g. blunt chest injury)
- Connective tissue disease (e.g. SLE)
- Bacterial infection.
- Rheumatic fever

ACUTE PERICARDITIS

Acute pericarditis may be infectious in origin or may be due to systemic disease. Viral pericarditis is most common. Symptoms or signs resulting from pericardial inflammation develop no more than 1-2 weeks duration.

CLINICAL FEATURES

General symptoms

Fever, sweating and chills etc. depending on the cause. Features related to pericarditis due to any cause may be chest pain and friction rub.

Chest pain:
Retrosternal chest pain, sharp in intensity, often radiating to the shoulders and neck. It is relieved by sitting forward and made worse by lying down. It is aggravated by movement, deep respiration or swallowing. The pain of pericarditis is almost always pleuritic. Associated symptoms with pain may be dyspnea, cough and occasionally hiccoughs.
Chest pain due to ischemia, pneumonia, pulmonary infarction or reflux esophagitis should be excluded.

Friction rub:
This is the diagnostic sign of pericarditis. Friction rub is a superficial scratching sound produced by movement of inflamed pericardium, localized to a small area over the precordium, best heard to the left of the lower sternum, usually in systole but may be audible in diastole. Friction is best heard when the patient leans forward, diaphragm of stethoscope is pressed firmly upon the chest, the patient's breath being held for a time in inspiration and then in expiration.

INVESTIGATION
- *ECG*: ST segment elevation with upward concavity. Later there may be T wave inversion.
- *Chest X-ray:* may show enlarged cardiac shadow if pericardial effusion is present.
- *Echocardiogram:* may show pericardial effusion.
- *Viral titer:* may be performed that show rising titer in case of viral pericarditis.

MANAGEMENT
One of the following anti-inflammatory drugs e.g.
- Ibuprofen (Brufen) 600 mg three- time daily for 2 weeks.
- Asirin 600-900 mg 6 hourly.
- Indomethacin 25-100 mg 4 hourly.
- Naproxen 500 mg 8 hourly.
- Corticosteroids: If pain response is inadequate with NSAIDs then add prednisolon 60 mg orally, daily for 2 days with tapering down to zero over a week. Oral colchicines 1mg daily may be the alternative to corticosteroids in patients not responding to NSAIDs.

VARIETIES OF PERICARDITIS

VIRAL PERICARDITIS
This may follow an upper respiratory tract infection and mostly caused by Coxsackie virus. Recovery occurs within few weeks.

BACTERIAL PERICARDITIS:
Bacterial pericarditis is usually characterized by purulent pericardial effusion. Direct extension from pneumonia or empyema is the most common source of infection, however it may spread through hematological route in case of bacteremia. Staphylococci, pneumococci and streptococci are the most common agents.

Clinical features:
High grade fever, shaking chills and tachycardia. Dyspnea or chest pain may be present. Friction rub is present in majority of patients. There may be rapid development of cardiac temponade.

Investigations:
- Pericardial fluid shows polymorphonuclear leukocytosis, low glucose, high protein, and elevated LDH, frank pus may be drained.
- X-ray shows cardiomegaly if effusion is sufficiently large..
- Echo shows pericardial effusion with or without adhesions.

Management:
- Fluid should be drained. Gram stain and culture of fluid should be sent. Culture of blood, urine, sputum and surgical wound should be performed.
- *Pericardial window:* purulent pericardial effusions are likely to recur; therefore surgical drainage with construction of pericardial window is often needed.

TUBERCULOUS PERICARDITIS
Tuberculous pericarditis may complicate pulmonary tuberculosis but may also be the first manifestation of the infection. (Tuberculosis is a very common cause of pericarditis, pericardial effusion and constrictive pericarditis in Pakistan).

Clinical features:

This is characterized by chronic low grade evening fever, weight loss and malaise associated with signs and symptoms of pericarditis. Large pericardial effusion develops in majority of cases presenting as paradoxical pulse, hepatomegaly, distended neck veins, pleural effusion, and distant heart sounds. Pericardium becomes thickened and may lead to constrictive pericarditis.

Investigations

- *Pericardial fluid aspiration and biopsy:* Diagnosis may be confirmed by aspiration of the fluid (pericardiocentesis) and direct examination or culture for tubercle bacilli but the yield is low. Yield of diagnosis is increased if pericardial biopsy is also performed with fluid aspiration. Pericardial biopsy shows either granulomas or organisms in 80-90% of cases.
- *Tuberculin test:* Positive tuberculin test increases suspicion, but negative test does not rule out tuberculosis.
- *Adenosine deaminase:* This enzyme is produced by WBC present in pericardial fluid, if it is elevated (> 40 units/lit) increases the sensitivity of 93% and specificity to 97% for tuberculous pericarditis.

Management

- Anti-tuberculous chemotherapy for 12 months.
- Corticosteroids may help to speed up the resolution of symptoms and decrease re-accumulation of fluid, but they do not influence the risk of death or progression to constrictive pericarditis.
- Open drainage (complete surgical drainage) reduces requirement of repeated pericardiocentesis and also decreases the risk of constrictive pericarditis.

Other types of pericarditis

- **Post-MI pericarditis:** pericarditis following myocardial infarction develops in first 1-3 days, treatment is aspirin 600mg 3-4 times daily for 2-5 days. NSAIDs and steroids should be avoided due risk of cardiac rupture.
- **Dressler's syndrome:** Post myocardial infarction syndrome or Dressler's syndrome occurs in 3-4% of patients as early as 1 week to a few months presenting with, fever, chest pain, arthralgia, and pericardial effusion. It is an autoimmune process. Treatment is aspirin or NSAIDs, a short course of steroid (prednisolone) may be given in non-responders to the above treatment.
- **Malignant pericarditis:** as a result of infiltration by carcinoma of bronchus, and breast and Hodgkin's disease.
- **Radiation pericarditis:** mediastinal and thoracic radiation for breast carcinoma, lymphoma and lung malignancies that may cause acute pericarditis or delayed reaction after 1-20 years presenting with pericardial effusion.
- **Autoimmune pericarditis:** due to rheumatoid arthritis, SLE, scleroderma.
- **Drug induced pericarditis:** procainamide, penicillin or cromolyn may be responsible.
- **Hypothyroid- associated pericarditis:** .about 25-35% patients of severe hypothyroidism may develop pericarditis and effusion.
- **Uremic pericarditis:** it occurs in renal failure.

PERICARDIAL EFFUSION

ETIOLOGY

Pericarditis due to any reason may cause pericardial effusion.

CLINICAL FEATURES

Symptoms

- Clinical features depend on volume of effusion and rapidity of accumulation.
- Symptoms of specific etiology may be present.
- Asymptomatic chronic effusions may be discovered on chest X-ray obtained for some unrelated reason.
- Small effusion or slowly developing large effusion (1-2 liters) may be without cardiac symptoms. However large effusion may compress the surrounding tissues causing dysphagia, dyspnea, cough, hiccups, hoarseness, nausea or a feeling of abdominal fullness.

- Rapid accumulation of even modest amount of fluid may be associated with temponade manifesting as life threatening hemodynamic compromise i.e. reduced cardiac output.

On examination

Without temponade

1. Apex beat may be difficult or impossible to palpate and the heart sounds are muffled in large effusion.
2. Friction rub may be heard but quieter than before fluid accumulation.
3. Bronchial breathing may be heard in left axilla or left lung base because of lung compression by large effusion.

Cardiac tamponade:

This refers to compression of the heart by a large effusion which interferes with diastolic filling resulting in reduced cardiac output.

Patient is usually uncomfortable with features of reduced cardiac output and shock such as tachycardia, cool extremities, peripheral cyanosis, and depressed conscious level.

Hypotension is usually present.

Pulsus paradoxus mostly present

Raised JVP with obliteration of 'y' descent.

INVESTIGATIONS

ECG:

ECG shows reduced voltage, electrical alternans indicates hemodynamically significant effusion.

X-ray chest:

Chest x-ray shows increasingly large globular heart.

Echocardiography:

Echocardiography demonstrates pericardial effusion. Diastolic collapse of right atrium and right ventricle is the most useful echo sign of temponade.

Cardiac cathterization

In temponade, cardiac catheterization reveals:

- Low cardiac output
- Elevated equal or near equal pressures in all four chambers.

MANAGEMENT

- Treatment of the cause.
- Pericardiocentesis (tapping of the fluid): It may be diagnostic or therapeutic to relieve symptoms from cardiac tamponade.

Needles is inserted just below the xiphoid process, insinuated deep to the left costal margin and then directed towards the left shoulder.

CONSTRICTIVE PERICARDITIS (CPC)

Constrictive pericarditis is due to progressive thickening, fibrosis and calcification of pericardium. The heart is encased in a solid shell and cannot fill properly.

ETIOLOGY

- Tuberculosis pericarditis
- Hemopericardium
- Viral pericarditis
- Rheumatoid arthritis
- Cardiac surgery
- Radiation therapy
- Idiopathic

CLINICAL FEATURES

Signs of systemic venous congestion

Ascites, dependent edema, hepatomegaly and raised JVP, congestion of GIT leads to anorexia and postprandial fullness.

Signs of impaired ventricular filling

- Markedly raised JVP with prominent "x' and 'y' descents.
- <u>Kussmaul's sign:</u> a paradoxal rise in JVP during inspiration (normally JVP decreases during inspiration.
- <u>Friedreich's sign:</u> raised JVP with sharp diastolic collapse.
- <u>Pulsus paradoxus:</u> an excessive fall in volume of pulse and blood pressure during inspiration.
- Pericardial knock: an early diastolic sound.

Features of left sided congestion

Dyspnea, orthopnea and cough may occur but are much less frequent.

DIFFERENTIAL DIAGNOSIS

- **Cardiac temponade**
- **Restrictive cardiomyopathy**
  Restrictive cardiomyopathy (left ventricular function is usually depressed in restrictive cardiomyopathy while normal in constrictive pericarditis). There is also equal diastolic pressure of all four chambers in constrictive pericarditis. Pericardial thickening and calcification also occurs in constrictive pericarditis but not in restrictive cardiomyopathy.

INVESTIGATIONS

- **X-ray chest:** shows relatively small heart with calcification on lateral film.
- **ECG:** shows low QRS voltages and T wave inversion.
- **Echocardiography:** shows thickened pericardium and relative immobility of the heart. Ventricular cavities are small with normal wall thickness and dilated aorta.
- **CT scan**: it is helpful in detecting the thickness and calcification of the pericardium.
- **Cardiac catheterization:** final diagnosis may depend on cardiac catheterization. It shows elevated and usually equal diastolic pressures in both ventricles.
- **Endomyocardial biopsy** performed at the time of catheterization may help to identify infiltrative cardiomyopathy.

TREATMENT

- Initial treatment consists of gentle diuresis. Surgical resection of the pericardium (pericardiectomy) is the definitive treatment for constrictive pericarditis.

ATRIAL MYXOMA

It is the commonest primary tumor of heart and tends to occur usually in middle-aged females.
It originates in the intraventricular septum, with over 80% growing into the left atrium and remaining in right atrim. It is a benign tumor but may embolize.

CLINICAL FEATURES

1. **Systemic illness:** fever, malaise, weight loss, leukocytosis, raised ESR. Picture is often confused with infective endocarditis, lymphoma, other cancers and autoimmune diseases.

2. **Features of blood flow obstruction:** tumor may grow to considerable size and produce symptoms by obstructing mitral flow such as episodic pulmonary edema especially occurring on an upright posture and signs of low cardiac output.
3. **Peripheral embolization:** causing pulmonary or systemic infarction.

ON EXAMINATION

- Diastolic sound or murmur similar to mitral stenosis due to motion of the tumor—called "**tumor plop**" (causing obstruction of mitral valve).
- Right sided myxomas may present with right sided heart failure.

INVESTIGATIONS

- Echocardiography
- MRI

MANAGEMENT

Surgical excision.

Note: MVP and atrial myxoma are favorite questions of theory paper.

ACUTE CIRCULATORY FAILURE (SHOCK

Shock is the term used to describe acute circulatory failure with critical impairment of tissue perfusion resulting in generalized cellular hypoxia. It can occur either because the function of the heart itself is impaired or because the heart is inadequately filled.

ETIOLOGY

Type of shock	Examples
Hypovolaemic shock Secondary to any condition provoking a major reduction in blood volume.	• Internal/external Hemorrhage • Severe burns • Acute pancreatitis • Dehydration (e.g. diabetic ketoacidosis).
Normovolemic shock Secondary to capillary damage arteriovenous shunting and inappropriate vasodilation	• Septic shock • Usually Gram-negative septicemia) • Anaphylactic shock
Cardiogenic shock Caused by any form of sever heart failure	• Myocardial infarction • Acute massive pulmonary embolism • Pericardial temponade

CLINICAL FEATURES

Hypovolaemic shock

1. Inadequate tissue perfusion

- Skin: cold, pale, cyanosis
- Kidneys: oliguria, anuria
- Brain: restlessness then confusion, coma

2. Increased sympathetic tone

- Tachycardia
- Sweating

3. Metabolic acidosis and tachypnea

ACUTE CIRCULATORY FAILURE: GENERAL FEATURES

- Hyotension (systolic BP < 100 mm Hg)
- Tachycardia (> 100 / min).
- Cold clammy skin
- Rapid shallow respiration
- Drowsiness, confusion, irritability
- Oliguria (urine output < 30 ml/hour).
- Elevated or reduced central venous pressure.

Cardiogenic shock

- General features of shock.
- Chest pain or signs of myocardial failure e.g. raised JVP, gallop rhythm, basal crepitations, pulmonary edema.
- ECG findings of myocardial infarction

Septic shock

- General features of shock.
- Fever and rigors (may be hypothermia).
- Warm skin due to cutaneous vasodilatation.

Anaphylactic shock

- General features
- Warm skin
- Urticaria, angiodema, bronchospasm, wheeze and facial edema.

MONITORING

- Blood pressure
- ECG
- Skin temperature
- Oxygen saturation
- Urinary flow
- Central venous pressure (CVP)
- Pumonary artery wedge pressure (PAWP).

MANAGEMENT

1. Maintain patent airway
2. Oxygen administration
3. Posture: head low position to increase filling pressure of right ventricle and raise cardiac output.
4. Determination of type of shock:
   - Cardiogenic: raised CVP (central venous pressure).
   - Hypovolaemic: Low CVP.

5. Expand circulatory volume (except in cardiogenic shock).
- Blood: for shock due to hemorrhage
- Saline or plasma: for fluid lost due to burn or dehydration.

6. *Antibiotics:* Those antibiotics are given that cover both gram-positive and gram-negative organisms for septic shock. The antibiotics are given initially as blind therapy which are then adjusted according to the culture and sensitivity report.

7. *Inotropic agents*: vasopressors are used to increase cardiac contractility in cardiogenic shock. These agents are dopamine, dobutamine and noradrenaline.

AORTIC ANEURYSM

An aortic aneurysm is a permanent localized dilatation of the aorta with a diameter of at least 1.5 times that of expected diameter.

ABDOMINAL ANEURYSM

Abdominal aneurysm is the most common aortic aneurysm and mostly occurs between renal and iliac arteries. At this level diameter of aorta is 2 cm and aneurysm is defined as an aortic diameter is more than 3 cm. Cause is usually atherosclerosis and is more common in old men.

CLINICAL FEATURES

Asymptomatic

- Majority of abdominal aneurysms are asymptomatic and detected on physical examination (showing prominent aortic pulsation) or on ultrasound or CT scan performed for other causes.
- Concomitant atherosclerotic occlusive disease of kidney and lower extremities is present in about 25% of cases.
- Popliteal artery aneurysms are present in 15% of patients with abdominal aneurysm and conversely more than 1/3 of patients with popliteal aneurysms have abdominal aortic aneurysm.

Symptomatic

Mid-abdominal or lower back pain (or both) in the presence of a prominent aortic pulsation may indicate rapid aneurismal growth, rupture or inflammatory aortic aneurysm.

Ruptured aneurysm

Patients with ruptured aneurysm present with severe back, abdominal or flank pain and hypotension. More than 90% patient die before reaching to hospital and only chance for survival is emergency surgical repair.

INVESTIGATIONS

Ultrasound abdomen

This is the investigation of choice. Annual ultrasound examination is recommended for aneurysm more than 3.5 cm.

Contrast CT

It gives exact size and relation with renal arteries. MRI may be performed if dye is not suitable due to renal insufficiency.

Aortography

Advised before elective repair of aneurysm.

TREATMENT

Medical treatment

Beta blockers and roxithromycin have been shown to reduce the expansion rate of small aneurysm.

Standard surgical repair

Surgical excision and synthetic graft replacement is the treatment of choice for aneurysm more than 5 cm. In asymptomatic patient elective surgery is advised when the aneurysm exceeds 5 cm. Urgent repair is required for symptomatic patient irrespective of size.

Endovascular repair

Endovasculai repair by aortic stenting may also be performed through femoral arteries.

ANEURYSM OF THORACIC AORTA

Aneurysms of thoracic aorta account for less than 10% of aortic aneurysm. Ascending aorta is usually involved in Marfan's syndrome while the aneurysm in arch of aorta and descending aorta is usually due to atherosclerosis.

CAUSES

Medial degeneration, atherosclerosis, hypertension, chronic dissection, vasculitis, syphilis, Marfan's syndrome and Ehler- Danlos syndrome.

CLINICAL FEATURES

Clinical features depend on size, position and growth rate of the aneurysm. Patient may be asymptomatic and diagnosed on investigations for other diseases.

Some patients develop pain in chest, back or neck. Large aneurysm exerts pressure on other organs as following:

- Dyspnea and stridor due to pressure on trachea.
- Dysphagea due to pressure on esophagus.
- Hoarseness due to pressure on left recurrent laryngeal nerve.
- Neck and arm edema due to pressure on superior vena cava.

Aortic regurgitation may occur in aneurysms of ascending aorta.

INVESTIGATIONS

Chest X-ray

It shows medistinal shadow.

CT scan chest

It is required to differentiate aneurysm from other mediastinal masses such as tumor, cyst, thymoma, and retrosternal goiter.

Aortography

It is required to check the involvement of vessels of arch of aorta.

Treatment

Control of hypertension and use of beta blockers slow the rate of expansion.
Surgery is indicated in the presence of symptoms, rapid expansion or size greater than 5 cm.

MISCELLANEOUS CARDIAC EQUIPMENTS AND PROCEDURES

CARDIAC PACEMAKER

Therapeutic cardiac pacing is employed in any patient with sustained symptomatic bradycardia. Bradycardia may be due to sick sinus syndrome or heart block. It is also employed in asymptomatic patients with Mobitz type II block or complete heart block.

Temporary pacing

In emergency temporary pacemaker is employed that may be transvenous pacing or transcutaneous pacing, if patient recovers then temporary pacemaker is usually removed within a week, if not then permanent pacemaker is implanted.

Permanent pacemaker

Permanent pacemaker may be single chamber in which electrical stimulus depolarizes right ventricle only; in dual chamber right atrium and ventricle both are depolarized. Single chamber costs about Rs. 65000 while dual chamber Rs.115000.

IMPLANTABLE CARDIOVERTER DEFIBRILLATOR (ICD)

The ICD recognizes ventricular tachycardia or fibrillation and automatically delivers pacing or a shock to the heart to cause cardioversion to sinus rhythm. These are small just like permanent pacemaker and may be implanted in the pectoral region.

Indications

Primary prevention

Patients at high risk for sudden death in whom sustained VT or VF have not occurred previously. These high risk patients are with nonsustained VT, ejection fraction < 35% and those in whom VT or VF is inducible during electrophysiologic testing.

Secondary prevention

Patients who have been successfully resuscitated from VT or VF and those with repeated symptomatic VT.

ELECTROPHYSIOLOGIC STUDY (EPS) AND CATHETER ABLATION

Cardiac arrhythmias occur intermittently and therefore difficult to identify. Invasive electrophysiologic testing allows one to induce the arrhythmia in Cath lab. to identify its site of origin, its mechanism and to assess the risk of spontaneous ventricular arrhythmias. Radiofrequency catheter ablation is employed for symptomatic tachyarrhythmias.

Indications for electrophysiologic study

- Sick sinus syndrome
- AV heart block especially 2:1 block
- Recurrent syncope
- SVT
- VT
- WPW syndrome

INTRA-AORTIC BALLOON PUMPING

This is the technique used to assist temporarily the failing left ventricle. A catheter with balloon at its tip is introduced through femoral artery and manipulated under fluoroscope so that the balloon lies in the descending aorta just below the aortic arch. The balloon is rhythmically inflated and deflated with carbon dioxide gas. Inflation of balloon is timed to occur during ventricular diastole to increase diastolic aortic pressure and consequently to improve coronary and cerebral blood flow. During systole balloon is deflated resulting in reduction in the resistance to left ventricular emptying.

Indications

- *Cardiogenic shock*: to improve cardiac output when there is transient or reversible depression of left ventricular dysfunction such as in patient of severe MR waiting for surgery, VSD after MI, or patient waiting for heart transplantation.
- *Unstable angina:* to improve coronary circulation and then stabilizes the patient to perform angioplasty or by-pass surgery.

All these procedures are being performed at National Institute of Cardiovascular Diseases (NICVD) Karachi.

HEART TRANSPLANTATION

Heart transplantation has become the treatment of choice for younger patients with severe intractable heart failure, whose life expectancy is less than 6 months and disease is refractory to aggressive medical or surgical treatment.. After transplantation one year survival is about 90% and 5- year survival about 75%. The availability of donors is limited. It is very expensive procedure and this facility is not available in Pakistan.

Contraindications

- Age >60 years
- Alcohol/ drug abuse
- Uncontrolled psychiatric illness
- Uncontrolled infection
- Severe renal/ liver failure
- High pulmonary vascular resistance
- Systemic disease with multiorgan involvement
- Recent thromboembolism
- Malignancy

Complications

- Graft rejection
- Infections
- Hypertension
- Hypercholesterolemia
- Malignancy
- Coronary atherosclerosis
- Complications of immunosuppressive therapy

CARDIAC ARRHYTHMIAS

An abnormality of cardiac rhythm is called cardiac arrhythmia. Arrhythmias may be supraventricular that arise from the atrium or atrioventricular junction, and ventricular which arise from the ventricles.

DISORDERS OF RATE AND RHYTHM

Ectopic rhythms

Supraventricular
- Ectopic beats
- Supraventricular tachycardia
- Atrial flutter
- Atrial fibrillation

Ventricular
- Ectopic beats
- Ventricular tachycardia
- Ventricular fibrillation

Heart block

Sinoatrial block

Atrioventricular block
- First degree heart block
- Second degree heart block (Mobitz type I and II).
- Third degree (complete) heart block.

VAUGHAN WILLIAM'S CLASSIFICATION OF ANTI-ARRHYTHMIC DRUGS

According to their effect on the intracellular action potential

Class I – membrane stabilizing agents (fast sodium channels blockers).
- **Ia:** Block sodium channel and prolong action potential-- quinidine, procainamide, disopyramide.
- **Ib:** Block sodium channel and shorten action potential-- lignocaine, mexiletine, phenytoin.
- **Ic:** Block sodium channel with no effect on action potential-- flecainide, propafenone.

Cass II – beta-adrenoreceptor antagonists
Propranolol, metoprolol, atenolol, -esmolol

Class III – drugs whose main effect is to prolong the action potential
Amiodarone, sotalol, Ibutilide, bretylium

Class IV – slow calcium channel blockers
Verapamil, diltiazem.

Class V---
Adenosine, digoxin

SINUS RHYTHM

The normal cardiac impulse is originated from sinus node. Its rate of discharge is controlled by autonomic nervous system; sympathetic system increases heart rate while the parasympathetic system decreases it.

SINUS ARRHYTHMIA

Sinus arrhythmia is a cyclic increase in normal heart rate with inspiration and decrease with expiration. It results from reflex changes in vagal influence on the normal pacemaker. Sinus arrhythmia is more marked in slow heart rate and it disappears with increased heart rate due to any cause. Sinus arrhythmia is common in young people. Enhancement of vagal tone with agents such as digoxin and morphine may cause sinus arrhythia. It becomes less prevalent with increasing age and in autonomic dysfunction such as in diabetic autonomic neuropathy.

SINUS BRADYCARDIA

A sinus rate of less then 60 beats per minute during the day or less than 50 beats per minute during sleep is known as sinus bradycardia.

CAUSES

Physiological
- In athletes
- During sleep

Pathological

Extrinsic causes
- Beta blockers, digoxin, verapamil
- Raised intracranial pressure
- Hypothyroidism
- Cholestatic jaundice
- Hypothermia

Intrinsic causes
- Fibrosis of sinus node (sick sinus syndrome)
- Acute ischemia or infarction of sinus node.

CLINICAL FEATURES
- Patient may be asymptomatic
- Severe bradycardia may cause weakness, confusion and syncope.
- Atrial and ventricular ectopics are more apt to occur with slow sinus rate.

TREATMENT

- Identification and treatment of cause.
- Temporary pacemaker in symptomatic bradycardia if there is reversible cause.
- Permanent pacemaker in symptomatic irreversible cause.
- Acute symptomatic bradycardia responds to atropine 0.6 mg i.v.

SINUS TACHYCARDIA

Resting sinus rate of more than 100 beats per minute is called sinus tachycardia.

CAUSES

Non-cardiac

Acute

- Fever
- Hypovolemia
- Pain
- Infection
- Exercise
- Emotion/ anxiety

Chronic

- Pregnancy
- Anemia
- Thyrotoxicosis
- Beta agonists e.g. salbutamol

Cardiac:

Heart failure with compensatory sinus tachycardia.

CLINICAL FEATURES

- Onset and termination of sinus tachycardia are gradual (in contrast to paroxysmal supraventricular tachycardia).
- Sinus tachycardia infrequently exceeds 160/min.
- Patients complain of palpitation

TREATMENT

- Treatment of the cause
- Symptomatic sinus tachycardia can be reduced with beta-blocker or calcium channel blocker such as verapamil (Calan).

PATHOLOGICAL BRADYCARDIA

SINUS NODE DISEASE (SICK SINUS SYNDROME)

Sick sinus yndrome is more common in elderly; however it can occur at any age.

Etiology

Degeneration, ischemia, infarction, sarcoidosis, amyloidosis and Chagas' disease.

Presentations

Sick sinus syndrome may present with a variety of arrhyhmias as following:

- Persistent sinus bradycardia not caused by drugs.
- Sinoatrial block (sinus arrest) as pauses on ECG.
- Paroxysmal supraventricular tachycardia, atrial fibrillation.
- *Tachy-brady syndrome:* Recurrent supraventricular tachycardia (atrial flutter or fibrillation) associated with bradyarrhthmias i-e tachycardia followed by long pauses.

Clinical features

- Most of the patients are elderly
- Asymptomatic
- Syncope, dizziness, confusion, palpitation, heart failure or angina.

Investigations

- ECG
- Holter monitoring: it is important to know whether the symptoms coincide with arrhythmias or not because these symptoms may occur due to other reasons.

Treatment:

1. Therapy in sick sinus syndrome should be reserved for the patients with ECG documentation of tachy or brady arrhythmias in association with symptoms.
2. Some patients manifest improvement in bradycardia, pauses and symptoms with oral theophylline.
3. Dual chamber permanent pacemaker (PPM) is the treatment of choice to prevent symptomatic bradycardia.
4. Treatment of tachycardia is only possible after implantation of permanent pacemaker because digoxin, verapamil, diltiazem or beta blockers used for control of tachycardia may exacerbate bradycardia.
5. Anticoagulants – because there is risk of thromboembolism.

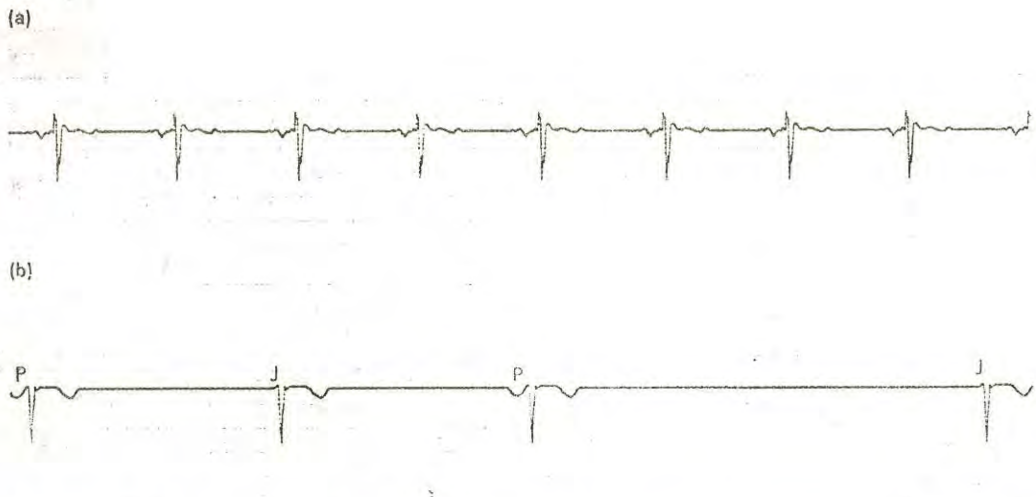


Fig. 13.33 **(a) An ECG showing normal sinus rhythm** (PR interval <0.2 s). P wave preceding each QRS complex. **(b) A patient with sick syndrome.** This shows sinus arrest (only occasional sinus P waves) and junctional escape beats (J). P waves are inverted in the cavity leads are shown here.

HEART BLOCK
(ATRIOVENTRICULAR (AV) BLOCK)

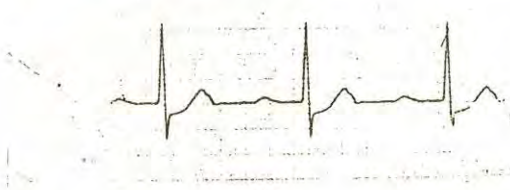
In this condition conduction between the atria and ventricle is impaired.

There are three forms of AV heart block

1. First degree heart block
2. Second degree (partial) heart block
3. Third degree (complete) heart block

FIRST-DEGREE HEART BLOCK

- It is simple prolongation of the PR interval to more than 0.22 second.
- Every impulse from the atria is conducted to the ventricle but with delay.



First-degree heart block implies prolonged conduction without block, each atrial impulse is conducted to the ventricles but there is delay in AV conduction leading to prolonged PR interval on ECG.

Site: The site of slowed conduction may be within the atrium, AV node, bundle of His or bundle branches.

Causes

- Enhanced vagal stimulation such as in inferior wall MI.
- Drugs e.g,. digitalis, beta blockers, verapamil, diltiazem and amiodarone.
- Myocarditis, Addison disease
- Congenital heart diseases such as ASD, Ebstein anomaly.
- Rheumatic fever
- It can also occur in normal individuals such as children and athelets.

Clinical features

It cannot be diagnosed clinically and its recognition depends on observing a PR interval of >0.20 s in ECG. It is a benign condition and requires no treatment; its only importance is as an index of drug toxicity and as a precursor of the more advanced degrees of heart block. Clinically, intensity of first heart sound is diminished in first-degree heart block.

> First degree and mobitz type I heart block develop due to increased vagal tone, drugs and ischemia or infarction of AV node. Prognosis is good in first-degree and in Mobitz type I, since reliable alternative pacemakers arise from the AV junction below the block if complete heart block develops.

SECOND DEGREE HEART BLOCK

Second-degree heart block implies intermittent conduction; some impulses from the atria are conducted to ventricles whereas others are not. There are three types of 2nd degree heart block.

Mobitz type 1: In this condition there is progressive lengthening of successive PR intervals followed by a dropped beat (nonconducted P). This is also known as Wenckebach's phenomenon. In this AV block there is conduction defect in AV node and AV conduction time (PR interval) progressively lengthens before the blocked beat. Pulse is irregular clinically. Prognosis is good in first-degree and in Mobitz type I, since reliable alternative pacemakers arise from the AV junction below the block if complete heart block develops.

Site of block is mainly AV node. QRS complex is normal in morphology (not wide) because there is no delay in intraventricular depolarization.

Causes:

- Inferior wall MI, acute rheumatic fever, myocarditis or degenerative conductive system disease.
- Drugs such as digitalis, beta-blocker and calcium antagonists.
- Hyperkalemia, in well trained athelets and during sleep.



Mobtiz type II: in this condition the PR interval of the conducted impulses remain constant but some P waves are not conducted (i.e. more P waves than QRS complexes).



Risk of progression to complete heart block is greater than in Mobitz type I.

Site of block is infranodal in location and QRS complexes are wide.

Mobitz type II AV block is abrupt and is not preceded by lengthening of AV conduction time. It is usually due to block within the bundle of His. Mobitz II block is almost always due to organic heart disease, in case it proceeds to complete heart block, alternative pacemakers are not reliable. Thus prophylactic ventricular pacing is required. Occasionally, the slow heart rate accompanying second-degree heart block is responsible for clinical deterioration and the heart rate must be accelerated by atropine or by artificial pacemaker.

2:1 block

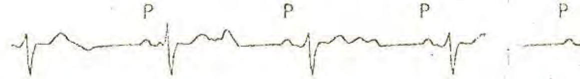
It may represent as either type Ior type II AV block in which there are two p waves to each QRS complex and therefore called 2:1 block. If PR interval is prolonged and QRS complex is narrow then it is type I second degree heart block. If PR is normal and QRS complex is wide (bundle branch pattern) then it is type II second degree AV block.



COMPLETE HEART BLOCK

Complete heart block is an advanced form of block. No impulse from atria reaches the ventricles. Cardiac action is maintained by an escape rhythm.

Escape rhythm arising in the bundle of His produces narrow QRS complexes at the rate of 50-60 beats per minute. Escape rhythm arising below the His bundle produces broad complexes and at the rate of 15-40 beats/min. Exercise does not increase the heart rate.



ETIOLOGY OF COMPLETE HEART BLOCK

Congenital

Acquired

- Idiopathic fibrosis
- Myocardial infarction / ischemia
- Infections: aortic root abscess in infective endocarditis, Chaga's disease, Lyme disease
- Infiltration: sarcoidosis, amyloidosis, neoplasia
- Trauma e.g. cardiac surgery
- Drugs e.g. digoxin, beta blockers, amiodarone
- Connective tissue disease: SLE, RA

It is a more advanced form of heart block due to lesion at the level of bundle of His or more often distally in purkinje system and associated with bilateral bundle branch block. QRS complex is wide and the ventricular rate is slower. Transmission of atrial pulses through AV node is completely blocked, and a ventricular pacemaker maintains a slow, regular ventricular rate, usually less than 45 beats/min. In chronic complete heart block pulse is slow (30-40/min) regular and does not vary with exercise. First heart sound varies in intensity, wide pulse pressure, changing systolic blood pressure. Patient may be asymptomatic or may complain of weakness or dyspnea if the heart rate is less than 35/min.

Episodes of ventricular asystole may occur during periods of transition from partial to complete heart block lasting several seconds to minutes. These episodes may cause cardiac syncope (also-called Adams-strokes attacks). These attacks often occur without warning, there is rapid loss of consciousness and the patient may fall. Convulsions may occur if the heart does not begin to beat again within about 10 seconds and the death will result if the arrest is prolonged.

SYMPTOMS OF HEART BLOCK

Symptoms of heart block develop due to bradycardia and loss of AV synchrony.

Exercise intolerance, easy fatigability, dyspnea on exertion, dizzy spells, near syncope and frank syncope

MANAGEMENT

Heart block complicating acute myocardial infarction

- Acute inferior wall myocardial infarction is often complicated by transient AV block which may respond to atropine 0.6mg I/V repeated as necessary, if it fails temporary pacemaker should be inserted. In majority AV block will resolve with in 7-10 days. Patient may develop heart failure or hypotension due to slow heart rate in already damaged heart requiring pacemaker.
- Mobitz II or complete heart block complicating anterior wall infarction is usually a sign of extensive myocardial damage and carries a poor prognosis. Asystole often occurs and a temporary pacemaker should be inserted prophylactically as soon as possible.
- If the patient presents with asystole, atropine (0.6mg I/V repeated if necessary) and isoprenaline (1-5mg in 500ml 5% dextrose infusion I/V at minimum rate) until a temporary pacemaker can be inserted.

Chronic heart block

1. Permanent Pacemaker- in patients with symptomatic bradyarrhythmias with complicating AV block.
2. Asymptomatic first degree or Mobitz type I second degree AV block does not require treatment.
3. Permanent pacemaker – in patients with asymptomatic Mobitz type II second degree or complete heart block.

BUNDLE BRANCH AND FASCICULAR BLOCKS

In the normal heart, each electrical impulse from the atria is conducted through the AV node to the bundle of His, from which it is then transmitted to the ventricles by the right and left bundle branches. The left bundle branch divides into two fascicles, the anterior and posterior fascicles. Therefore conduction system is composed of three fascicles:the right bundle, left anterior and left posterior fascicles.

Right bundle branch block (RBBB)

It presents electrocardiographically as:

- Wide QRS complex
- Broad, notched R waves (rsr, rsR or rSR patterns) in leads V1 and V2
- Wide and deep S waves in V5 and V6.

RBBB may be present occasionally in a person without heart disease, however usually it is caused by ischemic heart disease, congenital heart disease such as ASD, Ebstein anomaly, pulmonary hypertension, myocarditis or degenerative conduction system disease.

If there is no coronary heart disease, RBBB has benign course (no increased mortality) and requires no therapy. It becomes significant when present with acute MI and with bifascicular block.

Left bundle branch block (LBBB)

- It presents with wide QRS complex.
- Broad notched R wave in leads V5and V6 and usually in leads I and aVL.
- Small or absent R waves followed by deep S waves in leads V1 and V2

Left bundle branch block is rare in normal individual and is most commonly seen in ischemic heart disease. It indicates more severe disease. LBBB causes systolic and diastolic dysfunction and reduced ejection fraction. It is associated with significantly reduced long-term survival. Diagnosis of LVH or MI is difficult in the presence of LBBB.

Hemiblock

When there is blockage in anterior or posterior division of left bundle branch, it is called hemiblock.

Bifascicular block

RBBB plus left anterior or posterior hemiblock is called bifascicular block, in bifascicular and trifascicular block there are more chances to progress to complete heart block.

Trifascicular block

RBBB + hemiblock+ first degree heart block

PATHOLOGICAL TACHYCARDIA

ECTOPIC RHYTHM

When impulse arises somewhere other than the normal pacemaker SA node the rhythm is called ectopic rhythm: The ectopic rhythm may arise from:

1. Supraventricular (including atria, AV node or other AV junctional tissue)
2. Ventricular – in ventricle.

SUPRAVENTRICULAR ECTOPIC RHYTHM

ECTOPIC BEATS

- Mostly asymptomatic
- Can give the sensation of an extra or thumping beat.
- ECG shows a premature beat with a normal QRS complex.



SUPRAVENTRICULAR TACHYCARDIA (SVT)

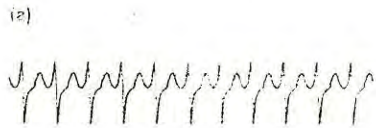
This is a tachycardia occurring in episodes with rate of 140-220, as a result of re-entry or rapidly firing ectopic focus in the atria or AV node. It may last from few seconds to many hours (if left untreated). Normally the heart is structurally normal in this condition.

Predisposing factors

- Anxiety
- Excess tobacco or coffee
- Hyperthyroidism
- Exertion
- Alcohol

Clinical features

- Patient feels that has suddenly started to beat fast (palpitation).
- Fainting, breathlessness and chest pain may occur.
- Polyuria is sometimes a feature
- ECG shows tachycardia with normal QRS complexes.



Management

In the absence of heart disease, serious side effects are rare. and most attacks break spontaneously. Terminate the attack if cardiac failure, syncope or anginal pain develops or if there is underlying cardiac or coronary disease.

Vagotonic maneuvers

Vagal stimulation blocks these arrhythmias to ventricle and terminates them. Vagal stimulation can be achieved by the following maneuvers.

- Carotid sinus message
- Pressure on eyes
- Valsalva maneuvers
- Self induced vomiting
- Breath holding
- Lowering the head between the knees.

Drugs

- Adenosine (Adenocor) 6 mg I.V bolus, if no response within 1-2 minutes second and third 12-mg bolus should be given. Side effects: bronchospasm, chest pain, flushing.
- Verapamil (Isoptin) 2.5-mg bolus, followed by additional doses of 2.5 mg to 5mg every 10 minutes up to total of 20mg can be given if blood pressure and rhythm are stable. Verapamil may be used initially or when the patient do not respond to adenosine. Oral verapamil 80-120 mg every 4-6 hour can be used in stable patient. Adenosine or verapamil can terminate attack in more than 90% of cases. Beta- blcockers and digoxin are less commonly used. If patient is hemodynamically unstable (in hypotension) then consider DC cardioversion before considering beta blocker or digoxin.
- Beta-blockers ismolol (Brevibloc) 500 microgram/kg IV within one minute followed by 25-200 microgram/min.
- Digoxin is also effective but it takes longer time to act. This can accelerate the tachycardia in patients with SVT with Wolff-Parkinson- White syndrome.

- Amiodarone (Cordarone) is usually not required for termination of attack, it is used for prevention of occurrence.

DC-cardioversion-in an emergency

If patient is hemodynamically unstable or if adenosine or verapamil are contraindicated or ineffective, synchronized electrical cardioversion should be performed. About 10-50 J are effective for termination of SVT.

Followup management

For patient with frequent ewpisodes of SVT, following medications may be effective in maintaining sinus rhythm during long-term therapy such as verapamil, diltiazem, digoxin or beta-blocker; if SVT is due to WPW syndrome then use amiodarone. If drug therapy is not effective then perform electrophysiologic study and perform catheter- mediated ablation.

WOLFF-PARKINSON-WHITE SYNDROME

WPW syndrome is a congenital condition caused by an abnormal myocardial connection between atrium and ventricle. In normal sinus rhythm conduction takes place through the AV node but in this condition it may bypass the AV node and conduct quickly over this abnormal connection to depolarize the ventricle abnormally. Because the bypass pathway lacks the rate-limiting properties of the normal AV node, the patients are at risk of ventricular fibrillation.

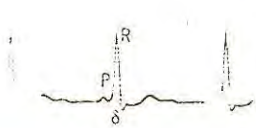
ASSOCIATIONS

- Sporadic in 95% of cases.
- Ebstein anomaly of tricuspid valve.
- Hypertrophic cardiomyopathy.

ECG shows:

- Short PR interval
- Wide QRS complex
- Delta wave: slurring of the beginning QRS complex.

(a)



SIGNIFICANCE AND CLINICAL FEATURES

WPW syndrome is found in all age groups from fetal and neonatal to elderly, more common in men. Most adults with WPW syndrome have normal hearts; some have associated Ebstein anomaly, MVP and cardiomyopathies. Patients may be asymptomatic and come to medical attention when a routine ECG shows WPW pattern. The term WPW syndrome is used when the patient having ECG pattern of WPW is symptomatic. Some patients present with recurrent episodes of palpitations, light-headedness, syncope or sudden death due to tachyarrhythmias.

Mechanism of uncontrolled tachycardia in WPW

In these patients atrial premature contractions have two pathways to enter the ventricles; one is normal AV node (that can block some impulses) and other one is accessory pathway (that is uncontrolled). If the premature impulse passes through AV node and return back atria through accessory pathway producing SVT with narrow QRS complexes (called *orthodromic tachycardia*). This tachycardia is under control (because AV node is under control), if the ectopic impulse passes through accessory pathway and returns back through AV node producing SVT with wide QRS complexes (called *antidromic tachycardia*), this conduction is not under control (because accessory pathway is not under control) all impulses are transferred to ventricles through accessory pathway (without blocking effect of AV node) leading to very rapid ventricular rate that may lead to vetntricular tachycardia or fibrillation.

Therefore always consider the possibility of WPW syndrome if patients present with fast ventricular rate.

TREATMENT

Asymptomatic person with only ECG abnormality requires no electrophysiological evaluation or treatment.

Termination of attack of tachycardia

Patient of WPW syndrome may present with tachyarrhythmias (SVT). Treatment depends on hemodynamic stability and whether the QRS complexes are wide or narrow.

Patient hemodynamically unstable

If patient of WPW presents with SVT and is hemodynamically unstable (hypotensive) then treatment of choice is DC cardioversion.

Patient hemodynamically stable

<u>*Narrow QRS complex:*</u> If QRS complexes are normal (not wide) then tachycardia should be treated in a manner similar to that of SVT without WPW syndrome with IV adenosine or verapamil. Atrial fibrillation with fast ventricular rate may occur with adenosine; therefore defibrillator should be available immediately.

<u>*Wide QRS complex:*</u> IV procainamide should be given. It blocks conduction to the ventricles via the accessory pathway, thereby slowing the heart rate and possibly converting to the sinus rhythm. In this situation if digitalis, verapamil or beta-blocker is given when

antegrade conduction occurs via accessory pathway. ventricular fibrillation may develop.

Prevention

Pharmacological treatment

For long-term therapy for prevention of recurrence combination of flecainide and propranolol may be effective. Amiodarone or sotalol may be given.
Digitalis shortens refractory period in accessory pathway and may lead to increased ventricular rate in patients of atrial fibrillation. Therefore digitalis should not be given to patient of WPW syndrome.

Radiofrequency ablation

Radiofrequency ablation of accessory pathway in electrophysiology laboratory is advised for patient with WPW syndrome with frequent tachyarrhythmias not fully controlled by drugs.

CAUSES OF ATRIAL ARRHYTHMIAS

- Ischemic heart disease
- Rheumatic heart disease
- Thyrotoxicosis
- Cardiomyopathy
- Lone atrial fibrillation (i.e. no cause discovered).
- Wolff-Parkinson-White syndrome
- Pneumonia
- Atrial septal defect.
- Carcinoma of the bronchus
- Pericarditis
- Pulmonary embolus
- Acute and chronic alcohol abuse.

ATRIAL FLUTTER

It is a condition in which a rapid atrial rate of round 300/min is associated with 2:1, 3:1 or 4:1 AV block. Most often, every second flutter beats conducts, giving a ventricular rate of 150 beats per minute. Occasionally every beat conducts, producing a heart rate of 300 beats per minute.

ECG: shows saw-toothed like atrial flutter waves.



Causes

Atrial flutter can occur as a result of atrial dilatation from septal defects, pulmonary emboli, mitral or tricuspid valve stenosis or regurgitation, heart failure or rarely without underlying heart disease. It may also occur in thyrotoxicosis, alcoholism, pericarditis, and following surgery for congenital heart disease. Occasionally it occurs with acute MI.

Clinical features

- Palpitation.
- Reduced cardiac output leads to fatigue, weakness, coolness of the skin, and light headedness. Inadequate coronary perfusion may cause angina, inadequate cerebral perfusion may lead to dizziness or syncope.

Management

1. DC cardioversion (at < 50 J) is usually the initial treatment of choice.
2. Pharmacologically ibutilide IV or procainamide can be given for cardioversion.
3. Rapid atrial pacing with a catheter in esophagus or right atrium can effectively terminate atrial flutter.
4. Verapamil may be used to slow the ventricular response.
5. Digitalis with betablocker or calcium channel blocker may be given to slow ventricular arte if electrical or pharmacological cardioversion is not possible.
6. Amiodarone can be tried in an attempt to restore sinus rhythm and prevent recurrence of atrial flutter.
7. Radiofrequency catheter ablation of atrial flutter is highly effective.

ATRIAL FIBRILLATION (AF)

Atrial fibrillation is continuous, rapid 400 or more beats per minute activation of the atria. The atria beat rapidly and ineffectively; the ventricles respond at irregular intervals giving the characteristic irregularly irregular pulse.

COMMON CAUSES OF ATRIAL FIBRILLATION	
• Coronary artery disease (including acute myocardial infarction) • Valvular heart disease (especially rheumatic mitral valve disease) • Idiopathic (lone atrial fibrillation) • Hypertension • Thyrotoxicosis	• Sinoatrial disease • Alcohol • Cardiomyopathy • Congenital heart disease • Pulmonary embolism • Pericardial disease • Pneumonia

ECG

- P wave absent
- Fine oscillation of baseline (fibrillation waves)
- QRS rhythm is rapid and irregular.



CLINICAL FEATURES

1. Palpitation
2. If ventricular response is rapid, cardiac output may fall resulting in:
   - Symptoms of pulmonary congestion (dyspnea, orthopnea and PND).
   - Symptoms of inadequate peripheral perfusion (angina, dizziness, syncope)
3. Systemic embolism (stroke, leg pain or abdominal pain)

MANAGEMENT

Electrical DC-cardioversion

Electrical DC-cardioversion if patient is unstable due to fast ventricular rate and presents in shock, severe hypotension, pulmonary edema or ongoing myocardial ischemia. The risk of thromboembolism is high if atrial fibrillation persists more than 48 hours.

Rate control strategy

In less unstable patients or those at particularly high risk for embolism due to cardioversion (such as mitral stenosis) rate control strategy is adopted instead of restoring to sinus rhythm. Digoxin, beta- blocker or verapamil will reduce the ventricular rate by increasing the degree of AV block and this alone may produce a striking improvement in overall cardiac function.

If rate control is unsuccessful and duration of atrial fibrillation is more than 2-3 days then perform transesophageal echo to look for thrombus, if there is no thrombus then cardiovert the patient, in case of presence of thrombus give anticoagulation for 4 weeks before and 4 weeks after cardioversion.

Elective cardioversion

First anticoagulate the patient for 4 weeks.
Pharmacological cardioversion by using amiodarone 300-400mg twice daily orally for 2-4 weeks then 200mg daily. Anticoagulation should be continued.

Refractory atrial fibrillation

Radiofrequency AV node ablation and insertion of permanent pacemaker may ensure rate control in resistant cases when no drug works.

Anticoagulants e.g. warfarin for a long time to reduce the systemic embolism in patients with atrial fibrillation. Only exception to anticoagulation is lone atrial fibrillation (when no cardiac cause for AF is identified, no hypertension, no coronary artery disease or diabetes).

VENTRICULAR ECTOPIC RHYTHMS

- Ventricular ectopic beats.
- Ventricular tachycardia
- Ventricular fibrillation.

VENTRICULAR ECTOPIC BEATS

The patient complaints of extra-beats, missed beats or heavy beats because it may be the premature beat, the post-ectopic pause or the next sinus beat that is noticed by the patient. The pulse is irregular; some early beats may not be felt at wrist.

ECG shows broad and bizarre QRS complex.



In normal heart they may be found in normal people often prominent at rest and disappear with exercise. No treatment is required; just beta-blocker may be given to reduce palpitation and anxiety.

In myocardial infarction frequent PVCs are observed but they are of no prognostic value and require no treatment. However persistent frequent PVCs (>10/h) indicate a poor long-term outcome. Anti - arrhythmic therapy does not improve the prognosis. In heart failure also PVCs are common but suppression with anti - arrhythmic drugs does not improve the prognosis; just treatment of heart failure may suppress these ectopic beats.

VENTRICULAR TACHYCARDIA (VT)

Ventricular tachycardia is defined as three or more consecutive PVCs. The usual rate is 160-240/min with regular rhythm.

Ventricular tachycardia is either non-sustained (lasting <30 sec) or sustained.
Patient may complain of palpitation, dyspnea, dizziness or syncope.

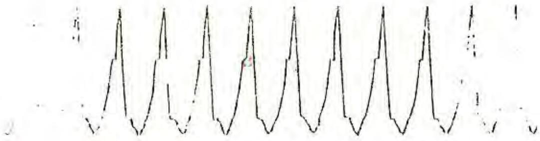
CAUSES

Ventricular tachycardia is associated with:

- Acute myocardial infarction
- Myocarditis
- Dilated cardiomyopathy
- Chronic ischemic heart disease
- Hypertrophic cardiomyopathy
- Mitral valve prolapse

ECG

ECG shows a rapid ventricular rhythm with broad, abnormal QRS complexes.



Torsade de pointes

It is a form of ventricular tachycardia in which QRS morphology twists around the baseline, may occur spontaneously in prolonged QT interval due to hypokalemia, hypomagnessemia or any drug that prolongs QT interval such as amitryptiline, quinidine, sotalol, chlorpromazine, macrolides and organophosphate insecticides. It has a poor prognosis.

TREATMENT

Ventricular tachycardia in acute MI

DC cardioversion

If the patient of MI with VT is hemodynamically unstable DC cardioversion is the only choice.

Lignocaine (Xylocaine)

In stable patient give lignocaine 1mg/kg IV bolus, if VT is not suppressed with lignocaine then give IV amiodarone (150 mg over 10 min followed by 360 mg over 6 hours and then 540 mg over 18 hours followed by 20-80 mg/kg/min infusion. Amiodarone is available by the name of Inj. Cordarone 150mg.

Chronic recurrent ventricular tachycardia

Sustained VT

Treatment of choice is implantable cardioverter-defibrillator device (ICD).

Non- sustained VT

- Beta blockers reduce the incidence of sudden death by 40-50%.
- Implantable cardioverter- defibrillator device (ICD) if sustained VT has been induced in electrophysiology lab.
- Amiodarone may be beneficial.

CARDIAC ARREST

Cardiac arrest is sudden and complete loss of cardiac function. It may be due to

1. Ventricular fibrillation
2. Asystole

VENTRICULAR FIBRILLATION (VF)

This is very rapid, irregular and ineffective ventricular activation which produce no pulse. Therefore patient is pulseless and rapidly becomes unconscious and respiration ceases.

Causes

1. Myocardial infarction
2. Electric shock
3. Hypokalemia
   - It is usually provoked by a ventricular ectopic beat (especially in acute MI) or ventricular tachycardia.

Clinical features

1. Loss of consciousness – within seconds
2. Pulse absent
3. Respiration ceases.

ECG shows

Shapeless rapid oscillations



Management

1. Electrical defibrillation. If it is not available then perform cardiopulmonary resuscitation procedure.
2. In survivors of VF if cause is not reversible, then implantable cardioverter- defibrillator is first line therapy to manage further episodes.

VENTRICULAR ASYSTOLE

In this condition there is no electrical activity of the ventricles. It may be due to a localized ventricular damage complicating the myocardial infarction. Treatment is cardiopulmonary resuscitation (CPR).

CARDIOPULMONARY RESUSCITATION (CPR)

Rapid treatment is necessary for cardiac arrest because irreversible brain damage will occur unless some circulation of oxygenated blood can be achieved within two or three minutes: after 3 minutes there will be permanent brain damage.

Cardiac arrest may result from ventricular fibrillation, pulseless ventricular tachycardia, asystole or electomechanical dissociation.

BASIC LIFE SUPPORT (BLS)

1. Confirm the diagnosis (unconscious, deaths like appearance, no pulse).
   - To confirm unconsciousness shake and shout at the patient.
   - To feel pulse carotid artery pulsation should be felt by pressing backward just to the side of thyroid cartilage.
2. If there is no pulse immediately call for help.
3. Quickly place the victim in an accessible position with firm underlying support (e.g. on his back on the floor) and begin basic life support which included ABC (airway, breathing circulation).

Airway

- Blood or mucus in the mouth should be removed
- Open the airway by extending the head and pulling the chin forward (head tilt and chin lift).

Breathing

Breathing of patient is assessed by looking the chest and abdominal movements and listening the breath sounds close to the victim's mouth and feel for airflow (look, listen and feel). If no evidence of breathing expired air respiration should be started: with the head of the victim tilted backwards and the chin pulled forward, the rescuer takes a deep breath and seals his lips around the mouth of the victim while pinching victim's nostrils, two effective breaths are given over 2 seconds each.

Circulation

Circulation is achieved by external chest compression. The heel of one hand is placed over the lower half of the victim's sternum and the heel of the second hand is placed over the first with fingers interlocked. The arms are kept straight and sternum is rhythmically depressed by 1.5 to 2 inches at a rate of approximately 100/min.. In this way thorax acts as a pump and the heart provides a system of one-way valve to ensure forward circulation. Respiration and compression is now continued as follows. Respiratory and circulatory support is continued by providing 2 effective breaths for every 15 cardiac compressions (15:2). This maintains adequate cerebral and coronary perfusion pressure.

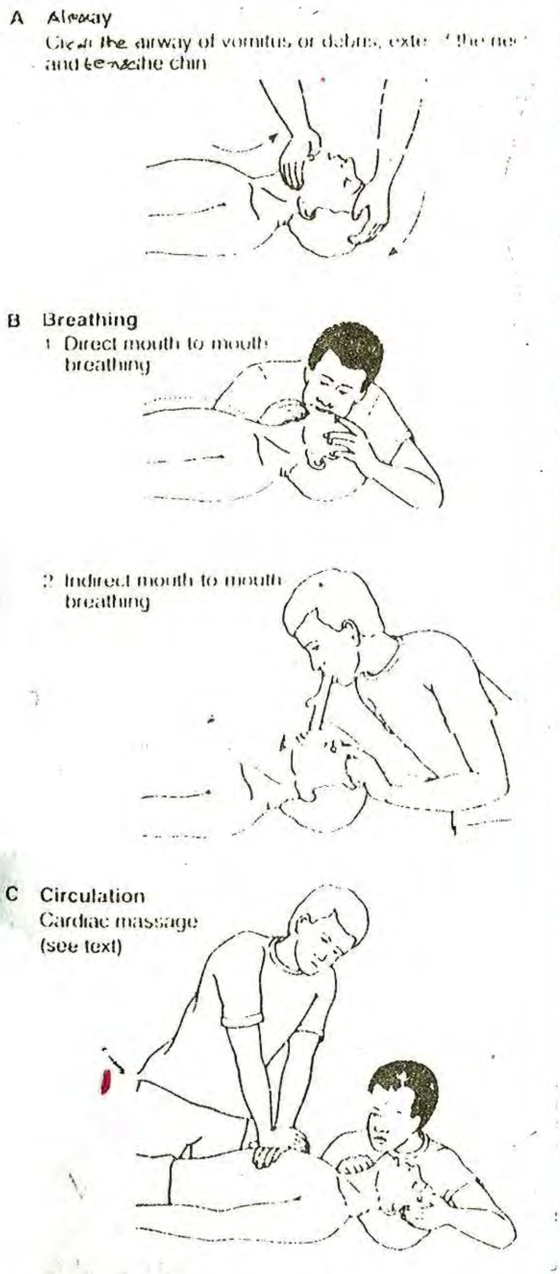


Fig. 5.40 Emergency resuscitation. The ABC of basic life support.

A. Airway. Clear the airway of vomitus or debris, extend the neck and raise the chin.

B. Breathing. 1 Direct mouth to mouth breathing; 2 Indirect mouth to mouth breathing

C. Circulation. Cardiac massage

ADVANCED CARDIAC LIFE SUPPORT (ACLS)

As the patient reaches to hospital proceed in the following sequence:

1. Assess the patient; patient unresponsive
2. Call for defibrillator and emergency trolley.

Primary ABCD

1. **A: Airway:** open the airway
2. **B: Breathing**: assess breathing: no breathing →give 2 breaths.
3. **C: Circulation:** Check carotid pulse—no pulse→ chest compressions.
4. **D: Defibrillation:** Continue CPR with chest compression until defibrillator is attached. If defibrillator is present in hand then start from checking the rhythm (that may be VT/VF, pulseless electrical activity or asystole) and defibrillation if appropriate.

Secondary ABCD

A: Airway: intubate at once

B: Breathing: confirm oxygenation and ventilation.

C: Circulation: pass IV canulla.

D: Differential diagnosis: search and treat identified reversible causes. There are 5H and 5T as following:

- Hypoxia (due to cardiac failure)
- Hypovolemia
- Hydrogen ion (acidosis)
- Hyper/hypokalemia
- Hypothermia

- Thrombosis, coronary (MI)
- Thrombosis , pulmonary (pulmonary embolism)
- Tension pneumothorax
- Temponade cardiac
- Tablets (drugs, accident)

Pulseless VT/VF

1. Give three shocks if VT/VF persists at 200 J, 300 J and 360 J.
2. If VT/VF persists after 3 shocks then continue CPR for one minute, during this one minute perform secondary ABCD
3. Give adrenaline 1mg IV then repeat adrenaline every 3-5 min
4. Defibrillate with 360 J within 30-60 sec
5. Give lignocaine 1.5mg iv stat. Repeat in 3-5 min to total loading dose of 3mg/kg or amiodarone or procainamide.
6. Consider buffer (soda bicarb)
7. Defibrillate 360 J 30-60 sec after each dose of medication—drug-shock-drug-shock.

PULSELESS ELECTRICAL ACTIVITY

Rhythm on monitor without detectable pulse

1. CPR with primary and secondary ABCD (but no defibrillation required)
2. Adrenaline 1 mg IV push and repeat every 3-5 min.
3. Atropine 1 mg IV (if rate is slow) repeat every 3-5 min to total dose of 0.04 mg/kg.
4. Continue CPR

ASYSTOLE

1. CPR with Primary and secondary ABCD (but no defibrillation).
2. Transcutaneous pacing
3. Adrenaline 1mg IV push and repeat every 3-5 min
4. Atropine 1mg IV and repeat every 3-5 min to total dose of 0.04 mg/kg.
5. Asystole persists- stop resuscitation in 5-10 min.

POST- RESUSCITATION CARE

- Examine CVS, respiration and CNS.
- Identify the complications of resuscitation e.g. rib fracture, pneumothorax, pericardial temponade, intra- abdominal trauma and misplaced tracheal tube.
- Laboratory tests: ECG, portable X-ray chest, ABGs, urea, creatinine, electrolytes.
- Anti- arrhythmia therapy to prevent recurrence.

MESSAGE FOR ALL

CPR is very important to save life in emergency, please learn proper CPR from your cardiology unit— unfortunately this is very neglected part of our training system. When you will save life with CPR you will be surprised and feel unforgettable happiness.

To learn medicine practically spend your final year in wards, work like a house officer. This is not fruitful to just listen some senior without practical involvement. Unfortunately we are not able to manage a patient after MBBS. Be practical, learn practically. Touch the patient, otherwise you will behesitant to examine the patient in examination, while the examiners watch your reflexes and speed to examine the patient in sequence just like a routine work.

GASTROENTEROLOGY 2

EXAMINATION OF ABDOMEN

POSITION OF THE PATIENT

The patient should lie flat, with one pillow under the head in order to relax the muscles of abdominal wall.

EXPOSURE

Abdomen should be exposed from xiphisternum to the pubis, leaving the chest and legs suitably covered.

INSPECTION

Shape of abdomen

- Normally full
- Scaphoid: a sunken abdomen due to starvation or wasting diseases.
- Protuberant: due to fat (gross obesity), fetus (pregnancy), flatus (gaseous distension due to intestinal obstruction), fluid (ascites).

Symmetry

- Normally symmetrical.
- Asymmetry may be due to visible bulge as a result of gross enlargement of liver, spleen, kidney or large tumors. Bulging may be central arising from the pelvis due to enlargement of uterus, ovary or bladder.

Movements

- Normally moving equally with respiration.
- Respiratory movements of abdomen usually cease in the presence of acute peritonitis

Umbilicus

- Normally central and inverted.
- Umbilicus displaced upward due to pregnancy and huge ovarian cyst.
- Umbilicus is flat or everted due to ascites.

Prominent veins

- Collateral veins visible due to inferior vena caval obstruction as a result of tumor or thrombosis, the direction of flow is upward towards the heart.
- Collateral veins due to cirrhosis radiate from umbilicus forming caput Medusa, the direction of flow is downwards towards the leg below the umbilicus.

Skin

Look for previous surgical scars, striae, and pigmentation. Striae develop due to stretch of abdominal wall causing rupture of the elastic fibers in the skin. Pregnancy, ascites, recent weight loss and Cushing's syndrome are the causes of striae formation.

Pulsations

Pulsation in the epigastrium is usually transmitted from the abdominal aorta. Less frequently it is caused by right ventricle, the liver, or an abdominal aneurysm.

Peristalsis

Peristalsis is prominent in small intestinal obstruction. Peristalsis due to pyloric stenosis may be visible as slow wave of movement passing across the upper abdomen from left to right. They may be present normally.

Hernias

Look for incisional hernias, epigastric, umbilical, femoral and inguinal hernias.

Inspection of abdomen at eye level

Squat down the beside the bed so that the patient's abdomen is at eye level, ask him to take slow and deep breaths through mouth and watch for any evidence of asymmetrical movement, indicating the presence of mass such as enlarged liver and spleen.

INSPECTION OF NORMAL ABDOMEN

On inspection abdomen is normally full, symmetrical, moving equally with respiration. Umbilicus is central and inverted. There is no scar, striae, pigmentation, prominent veins, pulsations or peristalsis. Hernial orifices are intact.

General principles

- Ensure that the examining hands are warm.
- If patient is in a low bed, sit on, or kneel bedside, the bed.
- Ask the patient if any particular area is tender and examine this area last.
- Encourage the patient to breathe gently through the mouth.
- If necessary, ask the patient to bend the knees to relax the abdominal wall muscles.
- Palpation can be divided into three phases: light, deep and during respiration.

Light palpation

Object

To note tenderness, guarding, rigidity and lump.

Method

- Place the examining hand on the abdomen and thereafter maintain continuous contact with the patient's abdominal wall.
- Note the tenderness and lumps in each region

Deep palpation

Object

To detect deeper masses and to define those already discovered.

Method

- Palpate the abdomen more deeply with the flat of the hand. If a mass is discovered describe its characteristics such as:
  - Site, size, tenderness
  - Surface which may be regular or irregular
  - Edges: which may be regular or irregular
  - Consistency: which may be hard or soft.
  - Mobility and movement with inspiration
  - Pulsatile or not
  - Whether one can get above the mass.

- *Guarding* of the abdomen is the resistance to palpation occurring due to contraction of abdominal muscles voluntarily or involuntarily.
- *Rigidity* is the constant involuntary contraction of the abdominal muscles always associated with tenderness and indicates peritoneal irritation.
- *Rebound tenderness* is said to be present when the abdominal wall having been compressed slowly, is released rapidly and a sudden stab of pain results. This may make the patient wince so the face should be watched while the manoeuvre is performed. It strongly suggests the presence of peritonitis.

Palpation during inspiration

The liver, spleen kidney and gall bladder should be examined during inspiration. The key success in visceral palpation is to keep the examining hand still and wait for the organ's edge to descend and strike during inspiration.

Liver

- Place the hand flat on the abdomen with the fingers pointing upwards and position the sensing fingers (index and middle) lateral to the rectus muscle.
- Press the hand firmly inward and upward and keep steady while the patient takes a deep breath through the mouth.
- If the liver edge is palpable describe its characters such as sharp or round, hard or soft, regular or irregular and non-tender or tender.
- Causes of tender hepatomegaly are hepatitis, liver abscess and congestion due to right heart failure.
- Now measure the ***liver span.*** Percuss from the fourth intercostal space downward and mark the upper border of liver identified when percussion note becomes dull from resonant, usually at the level of sixth rib. Now percuss from right iliac fossa upwards and mark the level where the lower border of liver is palpable. Measure this liver span that is usually 12-15 cm in midclavicular line. Span increases in hepatomegaly and decreases in cirrhosis.
- Liver may be palpable without hepatomegaly due to downward descent due to hyperinflation of lung in asthma and COPD.

Confirmation that the palpable mass is liver

- The mass is in the region of direction of enlargement of liver.
- Mass is moving with respiration.
- There is no gap between mass and costal margin and therefore finger can not be inserted between mass and the costal margin.
- Percussion note is dull over the mass.

Spleen

- Place the examining hand on the anterior abdominal wall with the fingertips well below the left costal margin, pressing inwards and upwards.
- Ask the patient to take deep breath, if spleen is enlarged it will hit the fingers during inspiration.
- If the spleen is not palpable, the patient must be rolled on the right side towards the examiner with left hip and knee flexed and palpation is repeated with the right hand while the left hand of examiner compressing left lower costal margin downwards.
- If spleen is still not palpable examine the patient from the left side, curling the fingers of the examining hand under the left costal margin as the patient breathes in deeply.

Confirmation that the palpable mass is spleen

- The mass is in the region of direction of enlargement of spleen.
- Mass is moving with respiration.
- There is no gap between mass and costal margin and therefore finger can not be inserted between mass and the costal margin.
- Percussion note is dull over the mass.

Features that confirm that the palpable mass is the kidney not the spleen

- There is a gap between mass and the costal margin.
- Fingers can be inserted between mass and costal margin.
- Mass can be palpable bimanually.
- Percussion note is resonant over the mass.

Kidney

- Use a bimanual technique to palpate the kidneys.
- Place one hand posteriorly below the lower rib cage and the other over the upper quadrant anteriorly.
- Push the both hands together firmly and feel the lower pole moving down between hands as the patient breathes in deeply.
- Push kidney back and forwards between the two hands- this is known as balloting
- Assess the size, surface, and consistency of palpable kidney.
- Examine the left kidney

PERCUSSION

Object

- To differentiate between abdominal distension due to ascites, gas, or cystic or solid tumor.
- To define the size and nature of organs and masses

General principles

- Percuss from resonant to dull area.
- Percuss the upper border of liver, and then measure the liver span.

Thrill

To detect the thrill, place a detecting hand on the patient's flank; flick the skin of the abdominal wall over the other flank using the forefinger. Thrill indicates large amount of ascitic fluid.

Shifting dullness

- Percussion should be started in the midline (with the fingers pointing towards the feet) then continue percussion towards the flanks until a dull note is obtained.
- Keep the finger in place as the patient rolls to the other side.
- Pause for about 10 seconds and percuss again. Ascites is suggested if the note becomes resonant and confirmed by obtaining a dull note while percussing back towards the umbilicus.
- Fluid thrill and shifting dullness indicate ascites.

Percussion of spleen

There are two methods for percussion of spleen; Nixon and Castell, .

Nixon method

The patient is placed to the right side so that the spleen lies above the colon and stomach. Percussion begins at the lower level of pulmonary resonance in posterior axillary line and proceeds perpendicularly toward the lower midanterior costal margin. The upper border of dullness is normally 6-8 cm above the costal margin. Dullness greater than 8 cm in an adult above the costal margin is presumed to indicate splenic enlargement.

Castell's method

With the patient supine, percussion in the lowest intercostals space in the anterior axillary line (8^{th} or 9^{th}) produces a resonant note if the spleen is normal insize. This is true during full inspiration or expiration. A dull percussion note on full inspiration suggests splenomegaly.

AUSCULTATION

- Place the diaphragm of stethoscope just below the umbilicus and auscultate for peristalsis bowel sounds for at last 3 minutes before deciding that they are absent (i.e. paralytic ileus).
- Auscultate liver for bruit (present in hepatoma)
- Auscultate for renal bruit on either side of the midline above the umbilicus that may be present in renal artery stenosis.
- Auscultate over the aorta for bruit.

INVESTIGATIONS OF GASTROINTESTINAL DISEASE

ENDOSCOPY

Fibreoptic endoscopy is used to examine the esophagus, stomach, duodenum and colon. Video endoscopy images can be displayed on color monitor.

Upper gastrointestinal endoscopy

After the patient has fasted for at least 4 hours, this is performed under local anesthetic throat spray. Esophagus, stomach, and first 2 parts of duodenum can be seen.

UPPER GASTROINTESTINAL ENDOSCOPY

Indications

- Dyspepsia (especially ages over 55 years)
- Upper abdominal pain
- Atypical chest pain
- Dysphagia
- Vomiting, weight loss
- Acute or chronic GI bleeding
- Duodenal biopsy in the investigation of malabsorption

Contraindications

- Atlantoaxial subluxation as in rheumatoid arthritis
- Severe shock
- Recent myocardial infarction, unstable angina, cardiac arrhythmia
- Severe respiratory disease

Complications

- Aspiration pneumonia
- Perforation
- Bleeding

Procedure

- Explain to the patient the nature of procedure.
- Get written consent.
- Tell the patient that pain due to air inflation may occur and therefore IV sedation may be given.
- Fasting for at least 4 hours.
- Throat is sprayed with lignocaine (Xylocaine).
- IV sedation for very anxious patient.
- The instrument (endoscope) is passed into the pharynx under direct vision, then down the esophagus into the stomach and duodenum.
- NPO for 90 min after procedure.

Sigmoidoscopy and colonoscopy

Sigmoidoscopy can be carried out either in the outpatient clinic using a 20cm rigid plastic sigmoidoscope or in the endoscopy suit using a 60cm flexible instrument following a disposable enema for bowel preparation. Ulcerative colitis and distal colorectal neoplasia can be seen with sigmoidoscope. After full bowel cleansing it is possible to examine the entire colon and often the terminal ileum using a longer colonoscope.

COLONOSCOPY
Indications
• Rectal bleeding • Anemia • Altered bowel habit • Suspected inflammatory bowel disease • Colorectal cancer surveillance
Contraindications
• Severe shock • Recent myocardial infarction, unstable angina, cardiac arrhythmia • Severe respiratory disease • Possible visceral perforation • Severe active ulcerative colitis
Complications
• Perforation • Bleeding • Cardiorespiratory depression due to sedation
Procedure
• Two days before the procedure, start a low residue diet. • On the day of procedure take clear fluids only • Intravenous sedation with a benzodiazepine • Instrument is passed under direct vision and maneuvered around to the cecum and the terminal ilium. • Observation is required for approximately 2 – hours following the procedure.

BARIUM CONTRAST STUDIES

Barium swallow

The esophagus is visualized as barium is swallowed in the upright and prone positions. Motility abnormalities as well as anatomical lesions can then be observed. Reflux of barium can be observed with patient tipped head down.

Indications

For the diagnosis of stricture, hiatus hernia, gastroesophageal reflux and motility disorder such as achalasia.

Double – contrast barium meal

This is performed to examine the stomach and duodenum. A small amount of barium is given together with effervescent granules or tablets to produce carbon dioxide so that a double contrast between air and barium is obtained.

Indications

Gastric ,duodenal ulcers
Gastric cancer
Gastric outlet obstruction

Small bowel follow- through

This is used to examine the small bowel. Barium is swallowed and allowed to pass into the small intestine through the jejunum and into the ileum. This technique is the only way to demonstrate gross anatomy of small intestine but takes several hours for completion of the procedure.

Indications

Malabsorption
Crohn's disease

Small bowel enema

A N/G tube is passed through the duodenum and a large volume of dilute barium is introduced.

Indications

This is the investigation of choice now for assessment of small bowel especially if stricture or obstruction is to be visualized. It takes less time as compared to small bowel follow- through.

Barium enema

Bowel is thoroughly cleaned with oral laxative. Barium and air are insufflated via rectal catheter and double contrast views are obtained of the entire colon.

Indications

Colonic tumors or polyps
Diverticulosis

PLAIN X- RAY ABDOMEN

- Gas under the right diaphragm in gut perforation
- Air fluid levels in intestinal obstruction.
- Megacolon in severe colitis.

ULTRASOUND

It is helpful in diagnosing:

- Acute abdomen e.g acute cholecystitis, appendicitis, pancreatitis, gallstones and liver abscess.
- Mesenteric thickening in abdominal tuberculosis.
- Visceromegaly
- Biliary tract dilatation
- Ultrasound guided needle biopsy and aspiration

Endoscpic ultrasound

A gastroscope containing ultrasound probe is used for esophageal and gastric wall thickening for staging of cancer.

CT SCAN

It is helpful in the diagnosis of:

- Thick bowel wall and mesentery
- Reteroperitoneal structures and aorta
- Perforated viscus
- Subdiaphragmatic abscess

MRI

It is helpful in the diagnosis of:

- Abscess around the anus, rectum and pelvis
- Hepatobiliary and pancreatic diseases

CAUSES OF ORAL PIGMENTATION

Non-neoplastic: dental amalgum tattoo, Peutz-Jeghers syndrome, Addison's disease, and lichen planus.

Neoplastic lesions: melanotic nevi, malignant melanoma

ORAL ULCERS

APHTHOUS ULCERS

Recurrent aphthous ulceration of oral mucosa is a common disorder of unknown etiology consisting of recurrent bouts of one or more rounded, superficial and painful ulcers recurring at interval of days to a few months. Aphthous ulcers are particularly common in women prior to menstruation. Ulcers may be minor (< 10mm that heal without scarring) or major (>20 mm that heal with scarring). Painful stage lasts 7-10 days and healing is completed in 1-3 weeks.

Differential diagnosis

Large and persistent aphthous ulcers should be differentiated from oral ulcers associated with systemic disorders such as Crohn's disease, ulcerative colitis, Coelic disease, SLE, Bahcet's disease, neutopenia, drug allergy (Stevens-Johnson syndrome), herpes simplex virus infection, pemphigus vulgaris and lichen planus.

CAUSES OF ORAL ULCERATION

1. **Apthous ulcers**
2. **Infection**
   - Fungal: candidiasis
   - Bacterial: Vincent's angina, syphilis
   - Viral: herpes simplex
3. **Gastrointestinal diseases**
   - Crohn's disease
   - Celiac disease
4. **Dermatological conditions**
   - Lichen planus
   - Pemphigoid
   - Pemphigus
5. **Drugs**
   - Hypersensitivity e.g. Stevens- Johnson syndrome
   - Ctotoxic drugs
6. **Systemic diseases**
   - SLE
   - Bachet's syndrome
7. **Tumors**
   - Carcinoma
   - Leukemia, Kaposi's sarcoma

Management

- *Local anesthetic:* Bonjella gel to relieve pain.
- *Mouth wash* such as Listrine gargle.
- *Topical corticosteroids* (triamcinolone acetonide 0.1 % ointment) not available in Pakistan.
- *Systemic steroids:* one week taper... prednisolone (40-60mg/d... ...ng course of successfully ... has been used
- *Azathioprin...* ...e can be tried in severe cases.

CAUSES OF PAROTID GLAND SWELLING

- Mumps
- Calculi in the parotid duct
- Diabetes mellitus
- Sarcoidosis
- Cirrhosis of liver especially due to alcoholism
- Sjogren's syndrome
- Parotitis (usually by staph. Aureus)
- Drugs: phenothiazines, propyl thiourecil.
- Viral infection.
- Tumor

CAUSES OF XEROSTMIA (DRY MOUTH)

- Sjogren's syndrome (usually associated with rheumatoid arthritis and SLE).
- Diuretics
- Antihitamines
- Tricyclic antidepressants
- Irradiation for head and neck
- Psychogenic
- Dehydration
- Shock
- Renal failure

Halitosis
It is burning sensation in mouth with clinically normal o...al mucosa, usually in middle-aged and elderly fema...es. Causes may be poor oral hygiene, anxiety, esopha...geal stricture and pulmonary sepsis.

VINCENT'S ANGINA

Vincent's angina is characterized by painful, deep sloughing ulcers principally affecting the gums and resulting from infection with Borrelia vincenti. Poor oral hygiene and malnutrition are predisposing factors. Broad – spectrum antibiotics and mouthwash are required.

ESOPHAGEAL DISORDERS

Symptoms of esophageal disorders

Dysphagia: difficulty in swallowing

Odynophagia: painful swallowing usually due to candidiasis and herpes simplex infection.

Heartburn: due to reflux esophagitis.

DYSPHAGIA

Difficulty in swallowing is called dysphagia. Causes of dysphagia may be as following:

Dysphagia for solids (mechanical dysphagia)

Intrinsic narrowing

- Be...nign esophageal stricture
- O... esophageal webs and schatzki's ring
- P... benign and malignant esophageal tumors.

Ext...insic compression

- Enlarged thyroid gland
- Cervical spondylosis
- Posterior mediastinal mass

Dysphagia for solids and liquids both (motor dysphagia)

- Scleroderma
- Achalasia
- Diffuse esophageal sphincter spasm
- Diabetic neuropathy
- Bulbar palsy

Early for liquid
Early inflammatory conditions e.g. stomatitis, tonsillitis.

INVESTIGATIONS

Upper GI endoscopy: : it is the investigation of first choice if mechanical obstruction is suspected.

Barium swallow: it is the investigation of first choice if motility disorder is suspected.

ETIOLOGY OF DYSPHAGIA

Oral (painful mastication)
- Oral malignancy
- Tonsilitis
- Herpes Simplex
- Aphthous ulceration
- Stomatitis

Pharyngeal
- Following cerebrovascular disease (stroke)
- Bulbar and pseudobulbar palsy
- Pharyngeal malignancy
- Myasthenia gravis
- Motor neuron disease
- Globus hystericus
- Pharyngeal diverticulum

Oesophagus

Motility disorders:
- Achalasia
- Diffuse spasm
- Chaga's disease
- Scleroderma
- Diabetes mellitus

Extrinsic pressure

Mediastinal mass lesiion
- Bronchogenic carcinnoma
- Dilated left atrium
- Aortic aneurysm
- Foreign bodies
- Goitre

Intrinsic lesion:
- Benign esophageal stricture
- Carcinoma (including carcinoma of cardia)

Webs and rings:
Lower esophageal ring

CAUSES OF IMPAIRED TASTE
- Xerostmia (dry mouth)
- Drugs: metronidazole, carbimazole, lithium and penicillamine.
- Radiation therapy of mouth
- Viral infections
- Sensory loss

ORAL & ESOPHAGEAL CANDIDIASIS

The fungus candida albicans is a normal mouth commensal but may proliferate and produce thrush in debilitated patients, patients receiving corticosteroids, broad spectrum antibiotics or cytotoxic drugs. White patches are seen on the tongue and buccal mucosa. Painful swallowing (odynophaagia) suggests pharyngeal and esophageal candidiasis.

Treatment
- *Nystatin* (Nilstat drops) 10-20 ml 6 hourly in mild to moderate cases.

For moderate to severe cases one of the following drugs should be used.
- *Ketokonazole* (Tab. Nizoral 200mg) 1-2 tab in a single dose daily.
  (Note: it should not be used with gastric acid suppressors such as H2- blockes or antacids)
- *Fluconazole* (Diflucan) 200mg first day then 100mg daily in a single dose for 7-10 days.

GASTRO - ESOPHAGEAL REFLUX DISEASE (GERD)

Gastro-oesophageal reflux disease develops when the esophageal mucosa is exposed to gastric contents for prolonged period of time, resulting in oesophagitis and heartburn.

PATHOGENISIS
Several mechanisms operate to prevents reflux of gastric contains into the oesophagus, the most important is the lower oesophageal spincter (LOS) because:
- It is situated below the diaphragm, the physiological effect of sphincter is reinforced by intra abdominal pressure.
- Oblique entry of the oesophagus to the stomach ensure that the intra abdominal oesophagus is closed when the stomach is distened.

When these anti – reflux mechanisms are lost and there is persistent exposure of the lower oesophagus to acid and pepsin or bile, it results in oesophagitis.

The following mechanisms are mainly involved in reflux oesophagitis:

Decreased lower esophageal sphincter tone

Normally the lower oesophageal sphincter (LOS) is tonically contracted, relaxing only during swallowing. In patients with GERD the resting tone is low and LOS tone fails to increase when lying flat as occurs in normal patients. LOS tone also fails to increase when intra-abdominal pressure is increased by tight clothing or pregnancy.

Defective esophageal motility

There is reduced oesophageal clearance of acid due to poor oesophageal peristalsis leading to increased acid exposure time.

Delayed esophageal emptying

Gastric emptying is delayed in patients with reflux oesophagitis, reason is unknown.

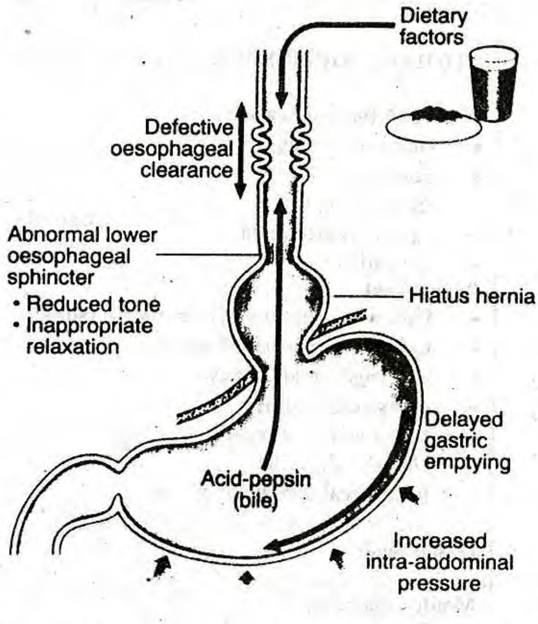
Hiatus hernia

Hiatus hernia means herniation of part of stomach into the chest.

There are two type of hiatus hernia

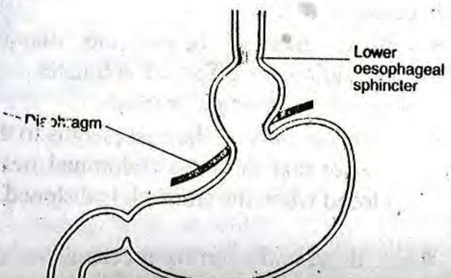
1. ***Sliding hiatus hernia:***
   In this condition the gastroesophageal junction slides through the hiatus so that it lies above the diaphragm.

2. ***Rolling or para – oesophageal hernia***
   In this condition a small part of stomach rolls up through the hernia along side the oesphagus, the sphincter remains below the diaphragm and remains competent.

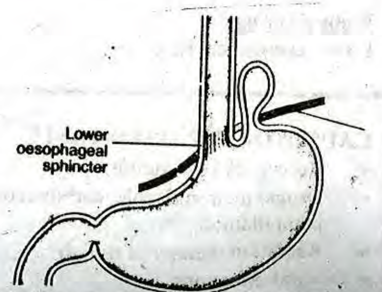


Factors associated with the development of gastro-oesophageal reflux disease.

Factors promoting Gastro-esophageal Reflux
• Pregnancy
• Obesity
• Fat, chocolate, coffee or alcohol ingestion
• Large meals
• Cigarette smoking
• Drugs: anticholinergics, calcium channel blockers, nitrates
• Systemic sclerosis
• After treatment for achalasia
• Hiatus hernia



Sliding



Rolling or para-oseophageal

CLINICAL FEATURES

1. ***Heart burn*** is the characteristic feature. It is felt as a deeply placed burning pain behind the sternum often radiating to the throat. It occurs after meal and is characteristically brought on by bending and by lifting or straining leading to increase in the intra abdominal pressure. It may also occur on lying down in bed at night and relived by sitting up and walking and with antacids .

2. ***Regurgitation of food*** into the mouth particularly when lying flat.

3. ***Iron deficiency anaemia:*** patient may present only with iron deficiency anaemia due to blood loss without symptoms of heartburn.

INVESTIGATIONS

Reflux esophagitis is usually a clinical diagnosis and in patients younger than 45 years investigations are not required unless some alarming symptoms are present such are dysphagia, weight loss, anorexia, hematemesis or melena.

For documantation of presence of reflux 24- hour intraluminal pH is monitored and barium swallow is performed. Manometry is performed to see the cause of reflux (esophageal dysmotility) and esophagoscopy is performed to see the complications of reflux.

1. 24 –hour intraluminal pH monitoring

When diagnosis is not clear on endoscopy this test is performed to confirm reflux. In this test the pH electrode is swallowed, positioned in the stomach, gradually withdrawn across the lower esophageal sphincter and fixed 5cm above the sphincter, intraluminal pH is recorded by a pH- sensitive probe. Diagnosis of reflux is made when pH does not rise as the electrode enters the esophagus from stomach and decrease in esophageal pH with straining maneuvers.

2. Manometry

This test is performed to see the esophageal motility disorder. A catheter is passed through the nose into esophagus and pressures are measured generated within the region of lower esophageal sphincter and body of esophagus either for a short time or up to 24 hours.

3. Barium swallow:

It is less sensitive than oesophagoscopy, however it shows hiatus hernia with reflux of barium.

4. Esophagoscopy:

It may show esophagitis, however mucosa may be normal even with severe symptoms. It also identifies the complications of reflux disease such as erosive esophagitis, ulcer, stricture or adenocarcinoma

COMPLICATIONS

Esophagitis

Esophagitis ranges from mild to severe causing ulceration with stricture formation. There is poor correlation between symptoms and histological and endoscopic findings. A normal endoscopy and normal esophageal histology may be present even with significant gastro-esophaageal reflux disease.

Benign esophageal strictures

Fibrous strictures develop as a consequence of long standing esophagitis. They present with dysphagia which is worse for solids than liquids. Diagnosis is made by endoscopy. Endoscopic ballon dilatation is undertaken, subsequently long term therapy with proton pump inhibitor such as omeperazole 20-40 mg daily is given to reduce recurrent esophagitis and stricture formation.

Barrett's oesophagus

Metaplasia of the normal squamous epithelium of the oesophagus to form columnar epithelium is known as barrett's oesophagus and is consequence of chronic gastroesophageal reflux. The risk of carcinoma is increased 90-150 fold.

Anemia

Iron deficiency anemia occurs as a consequence of chronic insidious blood loss from long standing oesophagitis.

Aspiration

Aspiration of gastric contents especially at night when patient lies down causes hoarseness of voice in the morning due to layrangeal edema. It may also lead to cough, aspiration pneumonia and lung fibrosis.

TREATMENT

GENERAL MEASURES

- Weight reduction
- Stop smoking
- Meals should be of small in volume
- Avoid alcohol, tea, fatty foods, coffee, chocolate, orange juice.
- Avoid heavy lifting and bending especially after meals.
- Avoid anticholinergic and calcium channel blockers.
- The head end of the bed should be elevated to 15° by keeping blocks below the head end of bed.
- Avoid late night meals to reduce reflux during sleep.

MEDICAL TREATMENT

Antacids

- Alginate containing antacid such as *GAVISCON* 10-20 ml after meals and at night is most commonly prescribed.
- A combination of magnisim trisilicate and aluminium hydroxide such as *Mucaine* 5 - 10ml 3 or 4 times daily before meals and at bed time.

Proton- pump inhibitor

Omeprazole (Losec 20mg) is a H+ K+ proton pump inhibitor causing reduction in gastric acid secretion and is used in moderate to severe cases. It may be needed for years.

H2 – receptor antagonists

- *Ranitidine* (Zantac 150 mg twice daily with meals and at bedtime upto 6 weeks.
- *Famotidine (Nocid 20mg)* twice daily.

Prokinetic drugs

These drugs increase peristalsis and speed up the gastric emptying.

- *Metoclopramide* (Maxolone) 10mg three times a day orally . It increases the contraction of lower oesophageal sphincter as well as promoting gastric emptying.
- *Domparidone* (Motilium) is a dopamine antagonist. It is given as one tablet 3 times daily half an hour before meal and is effective for promoting gastric emptying.

Eradication of Helicobacter pylori

Helicobacter pylori is associated with hypersecretion of gastric acid in some patients.Therefore 10-14 days treatment is given to eradicate Helicobacter pylori as following: Omeperazole (Cap. Losec 20mg) twice daily +Amoxicillin 1g twice daily +clarithromycin (Klaricid 250mg) twice daily.

SURGICAL TREATMENT

It is indicated if severe symptoms persist despite adequate medical therapy. The aim of surgery is to return the lower oesophageal sphincter to the abdomen by wrapping the gastric fundus around the esophagus (fundoplication).

ACHALASIA

Achalasia is a disease of an unknown etiology characterized by aperistalsis in the body of oesophagus and failure of relaxation of the lower esophageal sphincter on initiation of swallowing.

Therefore the food collects in capacious oesophagus resulting in dilatation of the oesophagus.

A similar picture is seen in Chagas' disease (American trypanosomiasis) due to damage of neural plexus of the gut.

PATHOGENESIS

Achalasia is characterized by a hypertonic lower oesophageal sphincter whish fails to relax in response to oesophageal swallowing wave. As the disease progresses the obstructed lower oesophagus dilates and peristalsis within the body of esophagus becomes less powerful. The failure of peristalsis is because of dgeneration of the ganglion cells in myenteric nerve plexus of the sphincter and body of oesophageal wall.

CLINICAL FEATURES

Achalasia usually develops in middle life, but can occur at any age. Patient prsents with:

Dysphagia

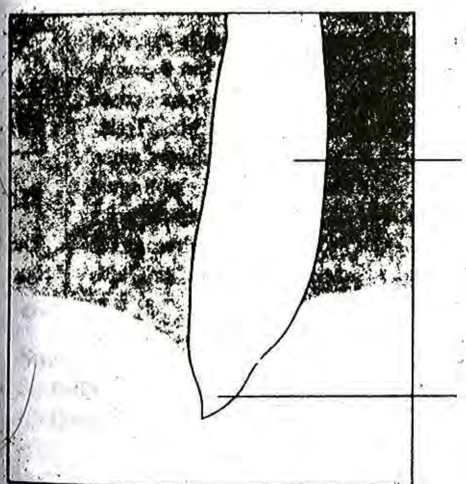
Intermittent dysphagia occurs for solids and liquids both. Occasionally food gets stuck that is overcomed by drinking water forcing the food to pass through the oesophagus.

Regurgitation

Regurgitation of food from the dilated oesophagus may be induced by the patient or may occur spontaneously particularly at night.

Retrosternal chest pain:

Severe reterosternal chest pain develops particularly in young patients due to oesophageal spasm.



INVESTIGATIONS

X ray chest

It may show dilated oesophagus with occasionally a fluid level behind the heart.

Barium swallow

It shows dilatation of the oesophagus and lack of peristalsis and collection of food. The lower end gradually narrows and this appearance (rat tail appearance) is due to failure of the sphincter to relax.

Oesophagoscopy:

It is necessary to exclude submucosal infiltrating carcinoma of the lower end of esophagus and esophageal stricture which can produce similar X- ray appearance.

Manometry

Diagnosis is confirmed by esophageal manometry.

- It shows pressure in esophagus greater than stomach due to fluid and food filled esophagus.
- Incomplete – relaxation of lower esophageal sphincter (<50%) while normal is more than 90% with swallowing.
- Absence of peristalsis of the esophageal body.

TREATMENT

Endoscopic

Pneumatic dilatation: Lower oesophageal sphincter is dilated forcibly using a pneumatic bag passed under x ray control. This weakens the sphincter.

Botulinum toxin injection: Endoscopic injection of botulinium toxin into the lower oesophageal sphincter results in marked reduction in sphincter pressure, but late relapse is common (> 50% within 6-9 month)

Surgical

Surgical division of the muscles at the lower end of the oesophagus (modified Heller cardiomyotomy) is performed if the endoscopic measures fail. This can be performed with laproscopy or open surgery. Reflux esophagitis is the main complication of surgery; therefore anti- reflux surgery (fundoplication) is also performed.

DIFFUSE OESOPHAGEAL SPASM

- This is severe form of abnormal esophageal motility that can produce reterosternal chest pain and dysphagia.
- Swallowing is accompanied by marked ocntractions of the esophagus without progression of the peristaltic waves.
- There are degenerative changes in vagus nerve.
- Emotional factor is also involved .
- Main symptom is pain, precipitated by emotion and eating. Pain is reterosternal, may be radiating to the back, neck, or arm, thus mimicing angina pectoris.

Barium swallow

Shows a hold up of barium in the oesophagus due to multiple uncoordinated contractions. The appearance resembles a "CORKSCREW".

Treatment

- Eating in a relaxed almosphere with adequate mastication.
- Nitroglycerine or nifedipine may relieve pain in some patients.

CARCINOMA OF OESOPHAGUS

Location & pathology

- Lower third 45% (squamous or adenocarcinoma)
- Middle third 40% (squamous cell carcinoma)
- Upper third 15% (squamous cell carcinoma)

SQUAMOUS CELL CARCINOMA

- Peak age over 50 years
- Male to female ratio 3:1
- Most common in China and Iran
- Important risk factors are heavy smoking and alcohol intake, N- nitroso compounds used in food preservatives. Fruits and vegetables decrease the risk.
- It occurs mainly in middle third and rarely in upper third of oesophagus.

RISK FACTORS FOR CARCINOMA ESOPHAGUS

Squamous cell carcinoma

- Tobacco smoking
- Heavy alcohol intake
- Plummer- Vinson syndrome
- Achalasia
- Celiac disease
- Tylosis: autosomal disorder in which there is hyperkeratosis of palms and soles.
- Vitamin deficient diet

Adenocarcinoma

- Long standing reflux esophagitis
- Barrett's esophagus

ADENOCARCINOMA

Adenocarcinoma usually arises in the columnar epithelium of lower third of oesophagus (in Barrett's oesophagus). This metaplasia (replacement of squamous epithelium with columnar epithelium) results from long-standing gastro-oesophageal reflux. Incidence of this tumor is increasing because of high prevalence of gastro-oesophageal reflux disease.

CLINICAL FEATURES OF ESOPHAGEAL CARCINOMA

Progressive dysphagia:

- Dysphagia is first intermittently and then regularly. The lesion is either ulcerative producing stricture in oesophagus or fungating causing obstruction of the lumen.
- Initially there is difficulty in swallowing of solids but later on dysphagia for liquids also develops.

Discomfort:

Discomfort at the site of obstruction occurs due to impaction of food.

Weight loss:

It results from dysphagia & anorexia

Fistula formation

Fistula formation between oesophagus and trachea results in coughing, pneumonia and pleural effusion.

SPREAD

- Direct invasion of surrounding structures and involvement of related lymph nodes is common as compared to widespread metastasis.
- Spread from middle third spreads to lymph nodes, larynx, thyroid, trachea and recurreent laryngeal nerve.
- From lower third it spreads to lymph nodes below the diapharagm and mediastinal lyph nodes.
- Distant metastasis occurs in lung, liver and bones.

INVESTIGATIONS

Oesophagoscopic biopsy

Upper GI endoscopy is the investigation of choice with biopsy and cytology.

Endoscopic ultrasound

This ultrasound is performed for assesment of depth of tumor and infiltration and for staging lymph node involvement.

Barium swallow:

Barium swallow shows gradually narrowing of lower end (rat tail appearance). This appearance may also be seen in benign stricture, oesophagitis and achalasia of the cardia.

X-ray chest & ultrasound abdomen

They may demonstrate metastasis in lung and liver.

CT scan

CT scan of thorax and abdomen are performed to assess local spread or metastasis for the staging of tumor and for assessing the possibility of surgery because surgery is only indicated if the tumor is confined to oesophagus..

MANAGEMENT

Management depends on the age and fitness of patient and the stage of the disease. Treatment consists of a combination of surgery, radiotherapy and chemotherapy.

Surgery

Surgery is considered in patients in whom tumor is confined to oesophagus and tumor has not infiltrated outside the esophageal wall. Unfortunately 90% of patients have extensive disease at presentation and inoperable.

Radiotherapy

- Squamous cell carcinoma of upper and middle thirds are treated with high voltage radiotherapy. Adenocarcinoma is less radiosensitive.
- For carcinoma of lower third, oesophagogastrectomy is performed. Surgery & pre operative radiotherapy may lead to enhanced survival.

Chemotherapy

Cisplatinum, 5-fluorouracil are being used before surgical resection in some centers with some prolongation of survival.

Palliative therapy

- Extensive tumours that are unsuitable for radical surgery or for intensive radiotherapy are treated by repeated dilatation of the stricture with insertion of a plastic or metalic tube (stent) into the oesophagus with the help of endoscope. This allows liquids and soft foods to be taken and is effective to relieve the most distressing problem of the patient.
- Tumor can be photocoagulated using a laser beam deliverd through endoscope or necrosed using alcohol injection.

PROGNOSIS

Five year survival :
Stage 1: 80%
Stage 2 30%
Stage 3: 18%
Stage 4: 04%
Most patients present in stage 3 and overall survival is 27% at 1 year and only 9% at 5 year.

CAUSES OF WEIGHT LOSS

- **Decreased intake:** anorexia, obstruction in esophagus or stomach due to stricture or infiltrating malignancy.
- **Increased metabolism:** hyperthyroidism, pheochromocytoma, and exercise.
- **Loss of energy in urine or stool:** diabetes mellitus, intestinal malabsorption.
- **Cancer:** especially GI, pancreatic and hepatic malignancies.
- **Infections:** tuberculosis, hepatitis, endocarditis, fungal disease, parasitic infestation and HIV.
- Depression
- Renal failure
- Hypercalcemia
- Pernicious anemia (causing anorexia).
- COPD
- CCF
- Chronic liver disease
- Parkinsonism

GASTRITIS & GASTROPATHY

Gastritis is the inflammation of gastric mucosa while gastropathy denotes condition in which there is epithelial or endothelial damage in the mucosa without inflammation. Gastritis may be erosive or nonerosive.

EROSIVE GASTRITIS

- *NSAIDS GASTRITIS:* Aspirin damages the mucosal barrier by allowing acid to diffuse into the gastric mucosa, where it causes the release of histamine that produces acute inflammation.
- *STRESS GASTRITIS:* Stress related gastric erosions develop within 18 hours in majority of critically ill patients producing stress ulcers. Major risk factors are trauma, burns (causing Curling ulcer), hypotension, sepsis, CNS injury, coagulopathy, mechanical ventilation, multiorgan failure, hepatic and renal failure. Prophylaxis with sucralfate or H2 receptor antagonists reduce the incidence of bleeding.
- *ALCOHOLIC GASTRITIS*
  Excessive alcohol consumption may lead to erosive gastritis and upper GI bleeding.

Clinical features of erosive gastritis.
1. It may be asymptomatic
2. If symptomatic-- anorexia, nausea, epigastric pain & heart burn may be the features.
3. If gastritis persists, a slow loss of blood may lead to anemia
4. The most common clinical manifestation is upper GI bleeding which may present as hematemesis or melena.

Portal hypertensive gastropathy
Portal hypertension results in gastric mucosal and submucosal congestion of capillaries and vanules. Bleeding may present suddenly with hematemesis or insidiously with iron deficiency. Therefore portal hypertension should be ruled out if patient presents with upper GI bleeding or melena. Beta-blocker propranolol is given prophylactically to reduce portal hypertension and prevention of bleeding.

Differential diagnosis of epigastric pain
- Peptic ulcer
- Gastroesophageal reflux disease
- Gastric cancer
- Biliary tract disease
- Pancreatic disease
- Food poisoning , viral gastroenteritis
- Functional dyspepsia

Investigations
Upper GI endoscopy (Gastroscopy).

Management of erosive gastritis
Treatment of the cause.

1. *NSAID –induced gastritis* is treated with stopping the drug, reducing the dose or administration with meals.
   If stopping the drug is not possible then add:
   - Omeprazole 20mg once daily or
   - Sucralfate 1g four times daily one hour before meal plus H2 –blocker such as famotidine 20mg daily or
   - Misoprostol (cytoprotective drug)
2. *Stress gastritis*
   - Prophylaxis: sucralfate or H2 –blocker in critically ill patients.
   - Bleeding: continuous intravenous infusion of H2 –blocker or proton pump inhibitor as well as sucralfate suspension.
3. *Portal hypertensive gastropathy*
   - Prophylaxis: propranolol (Inderal) to reduce portal pressure.
   - During bleeding : Octreotide (Sandostatin)

NONEROSIVE GASTRITIS

The diagnosis of nonerosive gastritis is based upon histologic assessment of mucosal biopsies; however endoscopy may be normal.

Types
1. Helicobacter pylori gastritis.
2. Pernicious anemia gastritis (autoimmune gastritis).
3. Menetrier's gastritis.

HELICOBACTER PYLORI GASTRITIS

It principally affects the antrum and is associated with the presence of Helicobacter pylori on the surface epithelium. This gram negative rod causes gastric mucosal inflammation.

PATHOLOGY

- Histologic assessment of biopsy shows presence of inflammatory cells such as lymphocytes and plasma cells. Inflammation may be confined to superficial gastric epithelium or may extend deeper into the gastric glands causing destruction of antral mucus glands leading to gastric atrophy.
- Intestinal metaplasia that may lead to dysplasia and ultimately carcinoma.

INVESTIGATIONS

Noninvasive testing for H pylori

1. Serological test

Anti- Helicobacter pylori antibodies (IgG) detection has sensitivity and specificity of over 90%. However this test does not indicate whether the infection is ongoing or not because IgG titer levels decline to undetectable levels in 50% of patients by 12- 18 months after eradication therapy.

Routinely this test is performed for screening purpose; if it is positive then further tests are performed to diagnose whether the infection is now active or not that usually requires endoscopy and mucosal biopsy for histologic detection of H. pylori.

2. Fecal antigen test

Detection of H. pylori antigen in stool has sensitivity and specificity of over 90%. Positive test is indicative of active infection.

3. ^{13}C Urea breath test

This test is also quick, sensitive and specific (over 90%). Positive test is indicative of active infection. The measurement of $^{13}CO_2$ in breath after ingestion of ^{13}C urea requires a mass spectrometer. This test is also used to demonstrate eradication of the organism following treatment.

Invasive testing for H pylori

Endoscopy

1. *Histology:*

Endoscopy is not indicated only for diagnosis of H. pylori in majority of cases because noninvasive tests are also sensitive; when this is performed it helps in detection of infection and other complications. Biopsy of gastric mucosa is obtained and H. pylori is detected histologically. Endoscopy also provides additional information about ulcers, reflux and identification of metaplasia or dysplasia on biopsy.

2. *Rapid urease test:*

Gastric biopsy is added to a urea solution containing phenol red. If H. pylori are present, the urease enzyme of H. pylori splits the urea to release ammonia which raises the pH of solution and causes a rapid color change. This test has sensitivity of more than 90% and is rapid mean for detection of H. pylori infection.

3. Culture and sensitivity

Biopsies obtained can be cultured on special medium and sensitivity to antibiotic can be ascertained, this test is most confirmative but it is rarely performed because of high failure rate, it is laborious and needs expertise.

Eradication Of H. Pylori Infection

The goal of treatment of H. Pylori positive duodenal or gastric ulcer is to heal the ulcer and eradicate (not suppress) the bacteria. Following are the regimen to eradicate the organism given for **10-14 days**. Proton pump inhibitor (PPI) such as omeprazole (Losec) should be continued for **6-8 weeks** to promote healing. Commonly used triple therapy regimen are the following:

Regimen 1

- Omeprazole (Losec) 20mg twice daily +
- Amoxycillin (Amoxyl) 1g twice daily +
- Clarithromycin (Klaricid) 500mg twice daily

Regimen 2

- Omeprazole (Losec) 20mg twice daily + Tetracycline 500 mg 4 times daily +
- Metronidazole 250mg 4 timese daily +
- Bismuth chelate (CEBE – S) 120mg 4 times daily

> **Practice Tips**
> In patient of dyspepsia, heart burn, epigastric pain where clinical diagnosis is gastritis or peptic ulcer and there is no history of NSAIDS intake---- anti- H. pylori antibodies are tested. In majority of cases endoscopy is performed and biopsy specimen is sent to lab for histologic detection of H. pylori. After eradication therapy for 10-14 days proton pump inhibitors (PPI) are continued for 6-8 weeks. If symptoms persist then fecal H. pylori antigen is tested to confirm the eradication of infection because treatment failure is not uncommon that requires another regimen.

PERNICIOUS ANEMIA GASTRITIS

It is an autoimmune disorder involving the fundic glands of stomach that secretes both the intrinsic factor and acid. The antibodies destroy the parietal cells with loss of acid and intrinsic factor.

Intrinsic factor deficiency leads to pernicious anemia because intrinsic factor is required for the absorption of vitamin B12.

Loss of acid secretion leads to achlorhydria. Achlorhydria leads to hypergastinemia that may lead to carcinoid tumors in about 5% of patients. The risk of gastric adenocarcinoma is increased 3-4 folds.

MENETRIER'S GASTRITIS

This is also called hypertophic gastropathy and consists of giant thickened gastric folds involving predominantly the body of stomach. Patients complain of nausea, epigastric pain, weight loss, and diarrhea. Because of protein loss through gastric mucosa patients develop severe hypoalbuminemia and anasarca. Etiology is unknown and treatment is symptomatic. Eradication of H. pylori may improve the patient.

PEPTIC ULCER

The term peptic ulcer applies to mucosal ulceration near the acid bearing regions of the gastrointeestinal tract.

SITES

Duodenum	90-95% of duodenal ulcers occur in the first portion of duodenum
Stomach	More than 90% of gastric ulcers occur in the lesser curvature.
Oesophagus	In reflux oesophagitis
Jejunum	In Zollinger- Elison syndrome
Meckle's diverticulum	Which contains ectopic gastric mucosa.

ETIOLOGY

1. Helicobacter pylori

It is the most important factor in peptic ulcer disease, accounting for 90% of duodenal ulcers and 70%of gastric ulcers.

2. NSAIDS

Aspirin and other non steroidal anti inflammatory agents damage the gastric mucosal barrier and are an important etiologic factor in 30% cases of gastric ulcer. These drugs are also responsible for very small proportion of duodenal ulcers. NSAIDs may also cause small intestinal ulcerations and perforations, colitis and colonic strictures.

RISK FACTORS FOR NSAID – INDUCED ULCER

- Age > 60years
- Past history of peptic ulcer
- Past history of adverse event in NSAIDs
- Concomitant corticosteroid use
- High dose or multiple NSAIDs
- Individual NSAID – highest with azaropazone, piroxicam, lower with ibuprofen

3. Heredity

Peptic ulcer tends to run in families. Two specific factors identified are:

- *Larger Parietal cell mass*
  With increased gastric acid output in patients with duodenal ulcer perhaps represents an inborn characteristic of the individual.

- *Blood group and blood group antigen*
  Those with blood group O and those unable to secrete their blood group antigen into the saliva and gastric juice are more predisposed to peptic ulceration.

4. Smoking

Smoking is an important risk factor. It also decreases the rate of healing and increases the risk of recurrence. Tobacco exerts its effects by stimulating acid secretion and impairing mucosal defenses by means of decreased blood flow and reduced prostaglandin synthesis.

5. Association with other diseases or known factors

- Higher incidence in patients with COPD, corpulmonale, cirrhosis, chronic renal failure.
- Steroids in high doses, severe burns
- Alcohol and dietary factors do not appear to cause peptic ulcer
- The role of stress is uncertain.

PATHOGENESIS

An ulcer forms when there is an imbalance between aggressive factors (e.g. acid and pepsin) and defense factors.

1. In peptic ulceration, initial damage to defensive mucosal barrier results from Helicobacter pylori infection, NSAIDS, smoking and other factors. This damage of mucosal barrier facilitates the damaging effect of acid and pepsin.

2. Ulcers occur only in the presence of acid and pepsin; they are never found in achlorhydric patients (i.e. no acid, no ulcer). Therefore we can say that aggressive factors (Helicobacter, NSAIDS, smoking) break the defensive mucosal barrier and then acid pepsin cause destruction and ulceration.

3. NSAIDs are non-selective inhibitors of prostaglandins by inhibiting both enzymes; cyclooxygenase (COX) 1 and 2. COX-1 is the principal enzyme involved in prostaglandin production in the gastric mucosa that has protective effect, while the COX-2 enzyme is involved in inflammatory prostaglandin production at the site of inflammation. Therefore these NSAIDs decrease inflammation and reduce pain along with decreasing the defensive mechanism of gastric mucosa and leave it susceptible to ulcerogenic effect of acid and pepsin.

4. Aspirin is the most ulcerogenic. Now the cyclooxigenase-2 (COX-2) inhibitors are available that selectively inhibit cyclooxygenase –2 enzyme and spare cyclooxygenase-1(COX-1). Examples are celecoxib, etodolac and nimesulide (Tab. Nise). Therefore it is recommonded that avoid NSAIDs in peptic ulcer patient, if necessary- use COX_2 inhibitors or lowest effective dose of ibuprofen (Brufen) or diclofenac sodium (Voren).

COMPARISION OF DUODENAL AND GASTRIC ULCERS

Duodenal ulcer

- It usually occurs in the first part of duodenum, 50% are on the anterior wall.
- Duodenal ulcer is virtually never malignant.
- More common 4 times than gastric ulcer.
- More common in male at age 30-55 years
- Risk factors: H Pylori, smoking, NSAIDS, COPD, cirrhosis, chronic renal failure

Gastric ulcer

- Most common cause NSAID use, other are bile reflux and H Pylori.
- Gastric ulcer may be malignant
- Less common than duodenal ulcer
- It usually occurs on the lesser curvature within the antrum or at the junction between body and antrum.

CLINICAL FEATURES

Peptic ulcer disease is a chronic condition with a natural history of spontaneous relapse and remission lasting for decades. Most patients have symptomatic periods lasting up to several weeks with intervals of months to years in which they are pain-free.

PAIN

1. **Site**: Epigastrium
2. **Character**: Burning in character
3. **Radiation**:
   Pain is localised and patient is able to point it with his one finger "pointing sign". If pain is radiating to the back in inter scapular region and not responding to antacids or other anti-ulcer drug, suggests posterior penetration of ulcer into the pancreas.
4. **Time of pain:**
   Soon after eating within 15-30 minutes in gastric ulcer while 2-3 hours after eating in duodenal ulcer that frquently awakens the patient at night.
5. **Relation with food:**
   Patient with gastric ulcer are afraid to eat because it causes pain due to release of acid in response to food. Patients with duodenal ulcer feel pain in empty stomach and get relief after taking food which causes partial neutralization of acid. Then in response to food there is increased acid secretion which causes pain after 2-3 hours. Acid induced pain is believed due to acid stimulation of chemical receptors.
6. **Aggravating factors:**
   - Smoking
   - Excessive intake of coffee and tea
   - Alcohol
   - Eating precipitates pain in gastric ulcer while missing a meal in duodenal ulcer.
7. **Relieving factors:**
   - Antacids and milk
   - Vomiting relieves pain in gastric ulcer
   - Intake of food relieves pain in duodenal ulcer
8. **Periodicity:**
   - Pain comes and goes in a 2-3 month cycle in gastric ulcer
   - In duodenal ulcer episode occurs with 4-6 month cycle, often worse in spring and autumn.
   - Relapse occurs more frequently in smokers than in non smokers.
9. **Duration of attack:**
   - A few weeks in gastric ulcer
   - A month or two in duodenal ulcer

VOMITING

Vomiting relieves pain of gastric ulcer and some patients force themselves to vomit after eating to relieve symptoms. It is uncommon in duodenal ulcer.

Other symptoms:

- Few patients present with haematemasis, due to perforation of the ulcer even in the absence of prior history of epigastric pain. Take history of melena also.
- Some patients may not have pain. They may complain of nausea and retrosternal burning.

ON CLINICAL EXAMINATION

Deep tenderness in epigastrium is present in most of the cases. Anemia may be present.

COMPLICATIONS

1. **Hemorrhage:**
   It occurs in 15-25% of patients, it is self limiting process however in some patients endoscopic intervention is required such as use of heater probe, electrocautry, laser photocoagulation, or injection of sclerosing agent to stop active bleeding or chances of rebleedig especially in whom there is visible vessel in ulcer.

2. **Perforation**
   Free perforation into the peritoneal cavity occurs in approximately 2-3 % of patients. Some patients have no prior ulcer symptoms.

3. **Penetration**
   Extension of the ulcer crater beyond the duodenal wall into contiguous structure e.g. pancreas especially if ulcer is in posterior wall. Less commonly ulcer may penetrate into liver, biliary tract or colon.

4. **Pyloric obstruction:**
   This may be caused by edema and spasm associated with an active ulcer, but it may also occur as a result of scar (fibrosis). Patient presents with abdominaal bloating, nausea, vomiting and weight loss.

D/D epigastric pain

Epigastric pain can also occur due to the following conditions.

- Atypical gastro-esophageal disease.
- Biliary tract disease.
- Acute pancreatitis
- Acute cholecystitis
- Choledocholithiasis
- Esophageal rupture
- Ruptured aortic aneurysm
- Acute myocardial infarction

INVESTIGATIONS

1. **Endoscopy:**
   Endoscopy is the procedure of choice for diagnosis of peptic ulcer because it is more accurate and has advantages that biopsy can be done for the detection of H pylori and malignancy (in gastric ulcer). All patients with gastric ulcer require biopsy initially and the follow up endoscopy and biopsy after 6 weeks of starting therapy, to confirm that the ulcer has healed.
   Malignant gastric ulcer is suspected on endoscopy if ulcer is larger, in greater curvature, ulcer in a definitive mass, friability of ulcer and easy tendecy to bleed.

2. **Barium meal (double contrast tachnique)**
   Barium meal is less commonly used now. It reveals gastric and duodenal ulcers. Endoscopy should be done if barium shows gastric ulcer to rule out malignancy.

MANAGEMENT

General Measures

- No smoking cigarette
- Avoid aspirin
- Avoid alcohol

Acid suppression

1. **H2 RECEPTOR ANTAGONISTS**

- These are competitive inhibitors of histamine at H2 receptors on the parietal cells.
- They are the first choice of therapy
- About 80 % duodenal ulcer heal with 4 weeks course, while the symptoms (e.g. epigastric pain) disappear within a few days of starting treatment.
- They can be given two times or a single night dose.
- All H2 antagonists are equally effective in reducing acid suppression and healing the ulcer when prescribed in recommended doses. They are different in potency but equal in efficacy.
- Although these drugs are generally safe, cimitidine can cause confusion in elderly and impotence and gynaecomastia in male, therefore should be avoided in young males and elderly.

- Ranitidine (Zantac) 150 mg BD or 300mg at night
- Cimitidine (Tagamet)400mg BD or 800mg at night.
- Famotidine (Nocid) 20 mg BD or 40 mg at night
- Nizatidine (ulcid) 150 mg BD or 300 mg at night

Side effects

- *Cimitidine* inhibits cytochrome P450 hepatic enzyme reducing the metabolism of certain drugs resulting in increase in their level, duration and pharmacological effect. These drugs are warfarin, phenytoin, theophylline. Cimitidine also has week antiandrogenic effect resulting in tender gynaecomastia and impotence.
- *Ranitidine* has little effect on P450 and no antiandrogenic effect.
- *Famotidine and nizatidine* have no effect on P450 and no antiandrogenic effect.

2. PROTON PUMP INHIBITORS (PPI)

These drugs are also called H+, K+ ATPase inhibitors. They bind with acid secreting enzyme called H, K – ATPase in parietal cells and inactivate it. This H+, K+ ATPase (proton pump) of apical membrane of parietal cells is the ultimate mediator of acid secretion.

Compared with H2 receptor antagonists, proton pump inhibitors provide faster pain relief and more rapid ulcer healing. They are the most powerful inhibitor of gastric secretion yet discovered. They inhibit over 90% of 24 hour acid secretion while H2 blocker less than 65% in standard dosages. They are also used in combination therapy for eradication of Helicobacter pylori and for the treatment of reflux esophagitis.

- Omeprazole (Cap. Losec) 20 mg / once a day before breakfast.
- Lansoprazole (Cap. Zoton) 30 mg / once a day before breakfast.
- Pentoprazole (Tab. Protium) 40mg / once a day before breakfast.

Mucosal Defense Factors

1. Tight junctions between epithelial cells which form a physical barrier to diffusing hydrogen ions.
2. Mucus layer on epithelial cells.
3. Bicarbonate secreted by epithelial cells.
4. Adequate blood supply of gastric mucosa, which prevents accumulation of hydrogen ion within mucosal cells.
5. Competent sphincters (pyloric and lower esophageal) block reflux of bile salts into the stomach and esophagus.

DRUGS ENHANCING MUCOSAL DEFENSES

1. Sucralfate (Ulsanic)

- It forms an adherent complex with proteins in the ulcer base and protects it from further digestion. Sucralfate also stimulates mucus, bicarbonate and prostaglandin production.
- The drug is not absorbed from GI tract and has no known systemic effects. Only side effect is constipation
- Dose Tab Ulsanic 1g or syp. Ulsanic 1TSF 4 times daily one hour before meals and bedtime.

2. Bismuth compounds (CEBE-S) 120 mg

- Bismuth promotes ulcer healing by forming a bismuth-protein coagulant which protects the ulcer from acid and pepsin digestion. It also stimulates mucosal bicarbonate and prostaglandin production.
- It is also a powerful antimicrobial agent against Helicobactor pylori.
- Dose: 2 tabs. twice daily.

3. Prostaglandin analogues

- Misoprostol is a prostaglandin analogue that promotes ulcer healing by stimulating mucus and bicarbonate secretion and inhibition of acid secretion.
- Abdominal pain and diarrhoea are side effects
- It is less effective than other anti ulcer drugs in the treatment of active ulcer, therefore it is

used only as a prophylactic agent to prevent NSAID induced ulcer in patient taking NSAID regularly e.g. in rheumatoid arthritis. A combination of diclofenac sodium (NSAID) and misoprostol is available by the name of Tab. Arthrotec.

Antacids

- Low dose magnesium and aluminium containing antacids promote ulcer healing through stimulation of gastric defense mechanism. Due to availability of other potent anti -ulcer drugs they are not used as first line agents in the treatment of acute ulcers.
- Because of rapid relief of ulcer symptoms (due to acid neutralization) they are commonly used for symptomatic relief (e.g. epigastric pain and burning).
- Syp. Mucaine 2TSF half an hour before meal

SURGICAL MANAGEMENT

INDICATIONS FOR SURGERY IN PEPTIC ULCER

Emergency
- Perforation
- Hemorrhage

Elective
- Complications e.g gastric outflow obstruction
- Recurrent ulcer following gastric surgery

TYPES OF OPERATIONS

1. Partial gastrectom
2. Vagotomy

Partial gastrectomy

The principle is to remove the antral area of stomach that secretes gastrin, since this in turn stimulates acid production. This operation is also of two types.

Billroth type I:

The lower part of stomach is removed and the stomach remnant is connected with duodenum. This is most common operation for gastric ulcer.

Advantages:
- Decreased recurrence rate.
- Low incidence of diarrhea.

Disadvantage:
- High operative mortality.
- Increased complications e.g. dumping.

Billroth type II:

It is now rarely performed, except for duodenal ulceration following a vagotomy. The stomach remnant is connected to the first loop of jejunum (gastroenterostomy) and the duodenum is closed.

Vagotomy

(cutting the fibres of vagus nerve)
Advantage: decreased operative mortality.
Disadvantage:. increasing recurrence rate
Following are the types of vagotomy operations:

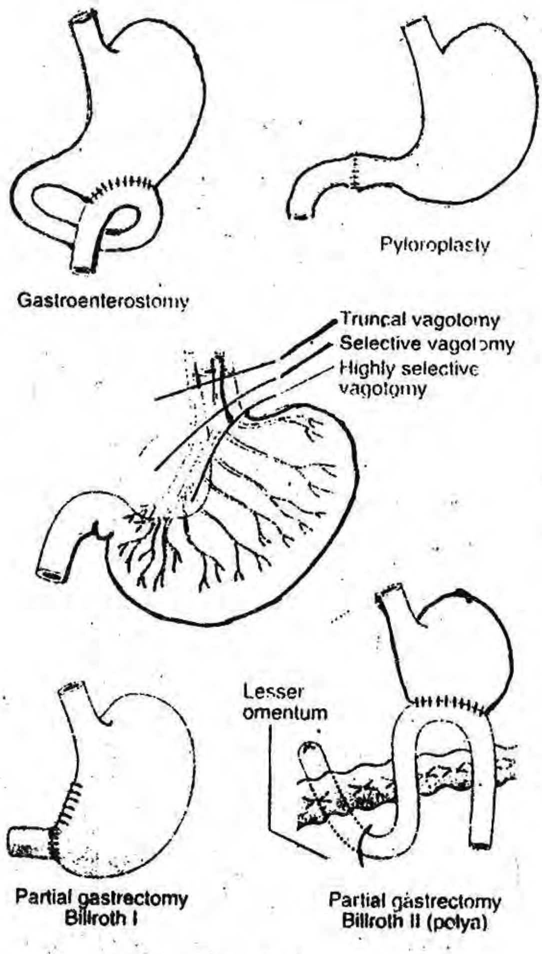
- *Truncal vagotomy* plus gastroenterostomy.
- *Selective vagotomy*: Preserving the hepatic and coeliac branch of vagus plus gastroenterostomy.
- *Highly selective Vagotomy:* Only the nerves supplying the parietal cells are transected. Recurrence rate is same as for above operations (5 –10%) but there is no diarrhea. This is now the commonest operation for duodenal ulcer

COMPLICATIONS OF SURGERY

1. ***Recurrence***
2. ***Dumping***:
   This is a term used to describe a number of upper abdominal symptoms e.g. nausea and distension associated with sweating, faintness and palpitations that occur following gastrectomy or gastroenterostomy. It is due to dumping of food into jejunum which is followed by rapid fluid dilution of the high osmotic load. Treatment is reassurance & symptomatic treatment.
3. ***Diarrhoea***:
   This is chiefly seen after vagotomy.
   Treatment: Antidiarrhoeal drugs e.g. codeine phosphate, Cholestyramine a resin that binds bile salts helps in some cases.

4. *Vomiting (bilious vomiting):*
   It occurs because food gets trapped due to altered anatomy.
   Treatment is symptomatic.

5. *Nutritional Complications*
   - Weight loss – due to anorexia
   - Anaemia – due to iron deficiency because of poor absorption. Treatment – oral iron (Tab. Iberet- folic 1 daily).



Operations for peptic ulcer.

ZOLLINGER – ELLISON SYNDROME (ZES)

This is an uncommon disorder in which severe peptic ulceration occurs due to gastric acid hypersecretion as a result of gastrin secreting gut neuroendocrine tumors (gastrinomas). Gastrinomas secrete large amounts of gastrin which stimulates the parietal cells of the stomach excessively, resulting in acid hypersecretion.

Primary gastrinomas may arise in pancreas (40%), duodenal wall (40%) or lymph nodes (5-15%). Over two thirds of gastrinomas are malignant. Less than 1% of peptic ulcer disease is caused by gastrinomas.

- Incidence: Mostly males between 30 – 60 years age.
- About 20-60%of patients have adenomas of parathyroid & pituitary glands also called Multiple Endocrine Neoplasia (MEN I).
- The tumor may be small (1mm) to large (20cm)
- The tumor may be benign or malignant. Malignant tumors are slow growing

CLINICAL FEATURES

1. Patients present with peptic ulcer indistinguishable from other causes of peptic ulcer. However ulcer symptoms may be more fulminant, progressive and persistent and respond poorly to usual medical and surgical peptic ulcer treatment.
2. Peptic ulcers due to Zollinger-Ellison syndrome may be single or multiple, usually located in the duodenal bulb, but may involve unusual sites such as post-bulbar duodenum, jejunum or esophagus.
3. Diarrhea may be the presenting feature even without ulcer symptoms. Diarrhea may occur secondary to acid hypersecretion as a result of inactivation of lipase (when the intraluminal pH of the small bowel falls below 6.5) thus interfering the fat digestion and causing diarrhea and steatorrhea. This diarrhea can be reduced or eliminated by aspiration of gastric juice.
4. Bleeding and perforation are common.

Zollinger-Ellison syndrome should be suspected in the following conditions.

- Peptic ulcer refractory to therapy
- Ulcers more than 2cm.
- Ulcers located to abnormal sites such as distal to duodenal bulb, jejunum or esophagus
- Multiple duodenal ulcers
- Frequent ulcer recurrence
- Ulcer occurring after ulcer surgery
- Ulcer associated with diarrhea
- Ulcer patient with hypercalcemia or family history of ulcers (suggesting MEN I)
- Patients with peptic ulcers who are H. pylori negative and those who are not taking NSAIDs.

INVESTIGATIONS

Fasting serum gastrin – Very high

Fasting serum gastrin is >150ng/L, usually 500-700 ng/L and as high as 450000ng/L (Normal level =20-50 ng L)

Measurement of basal gastric acid output

Basal gastric acid output is >4µmol/s

Serum calcium:

If increased, shows hypercalcemia due to hyperparathyroidism due to tumor of parathyroid gland if there is MEN 1.

Provocative tests

Secretin stimulation test

Intravenous secretin 2units/kg produces a rise in serum gastrin of over 200pg/ml within 2-30min in 85% patients of gastrinoma. Gastrin level remains same or slightly high in patient with common duodenal ulcer. (most sensitive provocative test for diagnosis of ZES.

Calcium infusion test

Intravenous infusion of calcium gluconate for 3 hours (5mg/kg/h). Serum gastrin is measured before and at 30 min interval for 4h. It stimulates gastrin usually more than 400 ng/L.

Endoscopy

Endoscopy shows large mucosal folds in stomach, duodenum and in some cases in esophagus also.

Imaging studies

Imaging studies are performed to localize the site of primary tumor and to detect metastasis.

CT, MRI and Ultrasound abdomen

Their sensitiveness is less than 50-70% for hepatic metastasis and 35% for primary tumors.

Somatostatin receptor scintigraphy and endoscopic ultrasound

These two tests in combination have sensitivity of >90% for detecting hepatic metastasis.

Investigations in Zollinger- Ellison syndrome

- Fasting serum gastrin >150ng/L
- Basal gastric acid secretion > 4µ mol/s
- Secretin stimulation test shows >200 pg/ml
- Calcium infusion test
- Serum calcium
- Endoscopy
- CT, MRI, ultrasound abdomen
- Somatostatin receptor scintigraphy and endoscopic ultrasound

DIFFERENTIAL DIAGNOSIS

Gastrinomas should be differentiated from other tumors of similar histopathology and that arise from gut or pancreas such as carcinoid, insulinoma, VIPoma, glucagonoma and somatostatinoma.

TREATMENT

Metastatic disease

If multiple hepatic metastases are present then main object is to control hypersecretion of acid with high doses of antisecretory drugs such as omeprazole (Losec) 40-120mg/d that causes ulcer healing. In some patients with isolated hepatic metastases surgical resection may decrease the need for antisecretory medication and may prolong survival. Due to slow growth of tumor 30% of patients with hepatic metastases have a survival of 10 years.

Localized disease

Gastrinoma can be resected before hepatic metastasis.

PROGNOSIS

- 10 years survival in 30% patients with hepatic metastasis .
- 15 year survival in over 80% patients who have no hepatic metastasis.

UPPER GASTROINTESTINAL BLEEDING

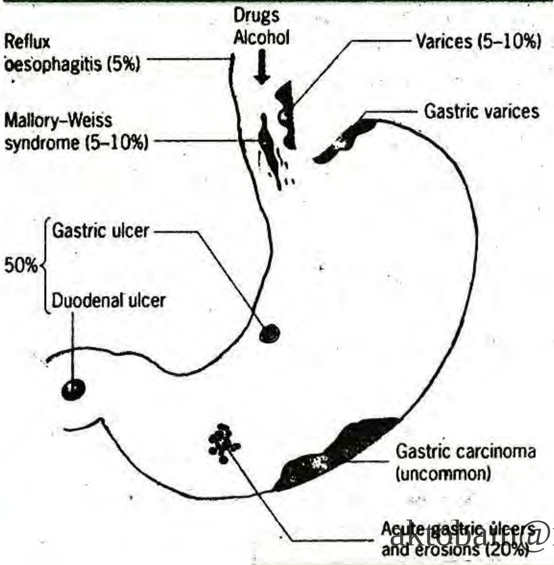
Bleeding from a lesion in the oesophagus, stomach or duodenum above the ligament of Treits is called upper GI bleeding. Bleeding from upper GIT may present with haematemesis or melena.

- ***Hematemesis*** means vomiting of blood
- ***Melena*** means passage of black tarry stools.
- Rapid bleeding presents as hematemesis while slow bleeding presents as melena
- Melena develops after as little as 50 - 100 ml of blood in the upper GIT. Black colour is due to altered blood by acid.
- If blood remains in stomach, it becomes partially digested and appears brown in the vomit called coffee ground vomiting.

ETIOLOGY

Common causes of upper gastrointestinal bleeding

Cause	%
Chronic duodenal ulcer	25
Chronic gastric ulcer	20
Gastric erosions (erosive gastritis)	20
Varices	10
Mallory-Weiss tear	7
Oesophagitis	5
Duodenal erosions	5
Cancer of the stomach	3
Miscellaneous	5



CLINICAL FEATURES

Clinical features depend on rapidity and amount of blood loss. Patient may present with vomiting of blood, melena or coffee ground vomiting.

SEVERE BLEEDING

Symptoms

- Weakness, faintness, nausea, sweating, restlessness and disorientation.

Signs

- Postural hypotension greater than 10 mm Hg is an indication of the loss of more than 20% of blood volume.
- Rapid pulse rate.
- Decreased urinary output.
- Patient may be in shock on arrival (systolic B.P < 90mm Hg)

INITIAL ASSESSMENT

Estimation of blood loss

1. Clinical judgement of degree or rate of bleeding.
2. B.P, pulse and postural changes.
3. Postural changes (orthostatic drop in systolic blood pressure of greater than 10 mm Hg or more; or a pulse rise of 20 beats / min or more indicates a 15 - 20 % acute loss of blood volume).
4. Monitor urine output because patient can develop acute renal failure due to hypovolemia.
5. Shock on arrival (systolic B.P. < 90mm Hg) indicates a massive 20 – 25% acute volume loss and is severe emergency.
6. The initial hemoglobin level and hematocrit will not alter until 24 - 72 hours until hemodilution has occurred. Therefore these tests are not important for the initial estimation of blood loss, but gives baseline hemoglobin level. A reduced hematocrit on admission to hospital suggests chronic bleeding prior to the acute episode.
7. A raised blood urea with a normal serum creatinine indicates loss of at least one liter.
8. The passage of a nasogastric tube (NG tube) is of value in assessing the persistent rate of bleeding.

SUBSEQUENT EVALUATION FOR THE CAUSE

- History of epigastric pain and heartburn may be present indicating peptic ulcer disease.
- Intake of NSAIDs or corticosteroids may give clue of gastric erosions.
- Liver cirrhosis is very common in Pakistan, therefore all patients should be examined for signs of chronic liver disease such as jaundice, palmer erythema, leukonychia, spider nevi, hepatosplenomegaly and ascites.
- History of forceful vomiting before hematomasis indicates Mallory-Weiss syndrome.

INVESTIGATIONS

1. Endoscopy:

Upper gastrointestinal endoscopy should be performed as soon as practically possible (when patient is hemodynamically stable) but urgently in patients with suspected esophageal varices or with continued bleeding. Endoscopy should be performed within 12-24 hours in virtually all cases. Endoscopy may be diagnostic and therapeutic.

Diagnostic

- To identify source of bleeding
- To determine the risk of rebleeding

Therapeutic:

Varices: 90% of actively bleeding esophageal varices can be effectively treated acutely with injection of a sclerosing agent (sclerotherapy).

Bleeding ulcer: All bleeding ulcers should be either injected with adrenaline around the bleeding vessels or direct cauterization of the vessel with heater probe or with laser therapy.

Risk of rebleeding in ulcer

In patients with peptic ulcer chances of re-bleed are as following:

- Non –bleeding ulcers under 2cm in size with clean base have less than 5% chance of rebleeding.
- Ulcers with flat red or black spot have less than 10% chance of rebleeding.
- Ulcers with firmly adherent clot have a 12 – 33% rebleeding risk.
- Ulcers with nonbleeding visible vessel has 50% risk of rebleeding.
- Ulcers with active bleeding have 80-90% chance of rebleeding.

2. Other investigations

- Blood CP
- Urea, creatinine, electrolytes
- LFTs, PT
- Blood grouping and cross matching

3. .Angiography

When bleeding is so rapid that the GI tract cannot be adequately examined by endoscopy, selective abdominal angiography may localize the site of bleeding. It may be diagnostic and therapeutic (to control bleeding).

4. Radionuclide Scan

A radionuclide scan with radiolabelled red cells may show the possible location of bleeding in patients in whom repeated endoscopy has failed to find the site.

MANAGEMENT

Intravenous access

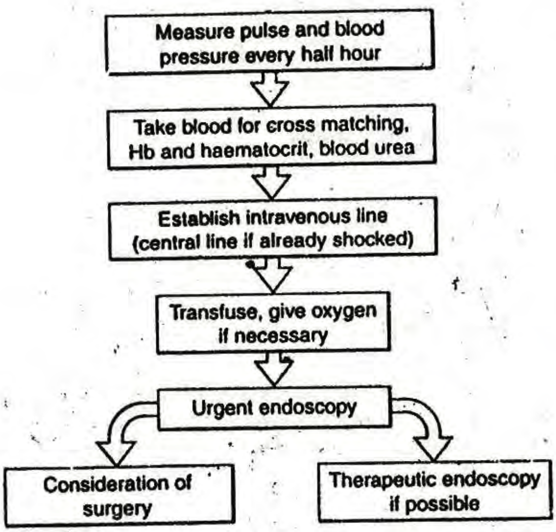
IV access with 18 gauge canulla to deal emergency.

Restoration of blood volume

Restoration of blood volume can be best achieved by transfusion of whole blood. Before blood arrangement restore blood volume with 0.9 % normal saline and plasma expander (Haemaccel). The rate of blood transfusion must be monitored carefully to avoid overtransfusion and consequent heart failure.

Sedation:

- Inj. Diazepam to control restlessness and anxiety
- Tranquilizers should not be given to hepatic disease because they may precipitate hepatic coma.
- Morphine should never be given because it may cause vomiting.



Therapeutic Endoscopy

Sclerosing and banding for varices and cauterization of bleeding vessels under direct vision in peptic ulcer.

H2 – receptor antagonists and proton pump inhibitors

H2-blockers are not effective in stopping active upper GI bleeding and should not be given. High dose of proton pump inhibitors such as omeperazole (Losec) 40mg BD for 5 days have been shown to reduce the risk of rebleeding in patients with peptic ulcer.

Octreotide (Sandostatin)

Continuous intravenous infusion of octreotide (100μg bolus followed by 50-100μg/h) reduces bleeding by decreasing splanchnic blood flow and therefore portal pressure in bleeding varices. Octreotide is not much effective for bleeding peptic ulcer.

Vasopressin

Intravenous vasopressin decreases splanchnic blood flow and portal pressure. It is generally reserved for patients with esophageal variceal bleeding that cannot be initially controlled with endoscopic intervention. Now octreotide is preferred on vasopressin to reduce portal hypertension because octreotide has no acute side effects.

Surgery

Indications for emergency surgery include:

- Severe bleeding or rebleeding that cannot be controlled by two endoscopic treatments.
- Massive hemorrhage when resuscitative efforts have failed.
- Need for more than 6 - 8 units of blood in the first 24 hours.
- Slow continuous bleeding for more than 48 hours.

> **Management of upper GI bleeding**
> - Intravenous access, oxygen, sedation
> - Blood volume replacement
> - Endoscopy
> - Pharmacological measures
>   - Proton pump inhibitor
>   - Octreotide
> - Surgery

Mallory – Weiss tear

This is a linear mucosal tear occurring at the esophagogastric junction and produced by a sudden increase in intra- abdominal pressure. it often occurs after a bout of coughing or retching. Hemorrhage may be large but usually stops spontaneously. Early endoscopy confirms diagnosis.

> **EMERGENCY MANAGEMENT OF ACUTE GASTROINTESTINAL BLEEDING**
> - History and examination
> - Monitor pulse and BP half- hourly.
> - Take blood for hemoglobin, urea, creatinine, electrolytes, grouping and cross matching (2 units initially).
> - IV line, central line if brisk bleed.
> - Normal saline/ blood transfusion
> - Indications for blood transfusion
>   Shock (BP <100, pulse > 100).
>   Hemoglobin <10 g/dl in patients with recent or active bleeding.
> - Oxygen for shocked patients.
> - Urgent endoscopy in shocked patients/ liver disease.
> - Re- endoscope for continued bleeding.
> - Surgery if bleeding persists.

LOWER GASTROINTESTINAL BLEEDING

Lower GI bleeding is defined as bleeding arising below the ligament of Treitz i.e. is the small intestine and colon. Majority of cases arise from colon and particularly the anorectal region.

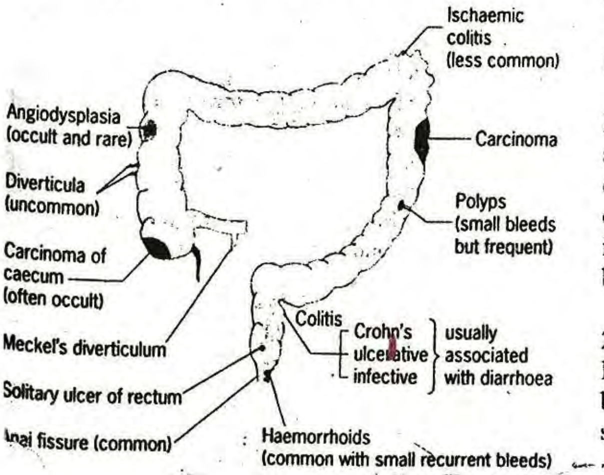
Hematochezia: means bright red blood per rectum

ETIOLOGY

Depending upon the age of patient and nature and severity of bleeding following are the common causes of lower GI bleeding.

1. **Young patients below 50 years:**
   - Anorectal disease e.g. hemorrhoids, anal fissure.
   - Infectious colitis: due to shigella, E.coli.
   - Inflammatory bowel disease e.g. ulcerative colitis.
2. **Old above 50 Years:**
   - Diverticulosis
   - Angiodysplasias.
   - Neoplasms
   - Ischemic Colitis

- **Bleeding with pain:** Anal fissure, ischemic colitis and inflammatory bowel disease.
- **Painless bleeding:** Internal hemorrhoids, diverticulosis, angiodysplasia.



EVALUATION OF PATIENT

Diverticulosis
Diverticulosis presents as painless maroon or bright red hematochezia in patients over 50 years of age. Bleeding stops spontaneously.

Angiodysplasia
Patients present with painless bleeding most commonly above the age of 70 years.

Neoplasm
Both benign polyps and carcinoma most commonly present with chronic occult blood loss or mild intermittent hematochezia.

Inflammatory bowel disease
Most commonly ulcerative colitis presents with diarrhea with occult blood or recurrent hematochezia. Abdominal pain, tenesmus and urgency are often present.

Anorectal disease
Hemorrhoids present as painless bleeding mixed with stool or dripping into the toilet bowl. There is painful small bleeding in case of anal fissure.

Ischemic colitis
Ischemic colitis is seen in elderly especially those who have atherosclerosis presenting as bloody diarrhea with mild abdominal cramps.

DIAGNOSIS

Diagnostic tools are used in the following sequence.

Rectal examination, anoscopy and sigmoidoscopy → nasogastric tube → Technetium scan → Angiography → Colonoscopy

1. **Rectal examination anoscopy and sigmoidoscopy:**

Digital examination anoscopy and sigmoidoscopy are performed to look for evidence of anorectal disease, inflammatory bowel disease or infections colitis. If source is identified, so further investigations are needed immediately unless bleeding persists or is recurrent.

2. **Exclude an upper tract source:**

Pass nasogastric tube in patients with significant bleeding to look for evidence of an upper GI source.

3. Technetium – 99m RBC Scan:
It should be performed in active bleeding to detect the source of bleeding. It can also detect intermittent bleeding because the patient can be monitored for GI bleeding for up to 24 hours.

4. Angiography
With active bleeding angiography is the diagnostic procedure of choice. It is also indicated if the hemodynamic stability is difficult to maintain due to massive bleeding. This test allows rapid localization and potential treatment of bleeding lesions.

5. Colonoscopy
It should be performed if bleeding stops or occurs at slow rate therefore a patient can be prepared for endoscopic examination. Colonscopy allows identification of angiodysplasia, tissue biopsy and therapeutic intervention with electrocautery heater probe or laser therapy of active bleeding. Colonscopy is not helpful during massive bleeding.

MANAGEMENT

1. Bed rest, sedation, and transfusion.
2. Stop aspirin and other NSAIDs.
3. *Therapeutic colonoscopy:* endoscopic electrocoagulation of angiodysplasia – if bleeding continues and colonoscopy is performed.
4. *Intra – arterial vasopression or embolization:* If bleeding site is localized by angiography, intra-arterial vasopressin may stop bleeding in 90% cases with active bleeding from diverticulum or angiodysplasia.
5. *Surgery:* Continuous bleeding unresponsive to the above measures requires surgical resection.

OCCULT GASTROINTESTINAL BLEEDING

Occult gastrointestinal bleeding is the loss of small amounts of blood into GI tract which is present in stool but cannot be seen (no hematochezia or melena). It is typically detected in one of the two settings.

- Positive fecal occult blood test or
- The presence of iron deficiency anemia in an adult.

Etiology:
All causes of upper and lower GI bleeding may also cause occult bleeding; following are the common causes.

1. *Tumors:* Benign or malignant tumor of any sites in GIT especially colon cancer.
2. Peptic ulcer and esophagitis
3. Non-steroidal anti-inflammatory drugs
4. Angiodysplasia
5. Infections: e.g. hook worm (most common cause)

Investigations

<u>Diagnosis of occult bleeding</u>

Fecal occult blood testing: Occult bleeding may be detected by card test for hemoglobin peroxidase (Guaiac test). It is an important means of finding colorectal neoplasia at earlier stage.

- ❑ <u>*False positive test:*</u> due to dietary peroxidases, undercooked meat, any cause of upper or lower GI bleed. Therefore patient should be tested on higher fiber and low meat diet with no ingestion of NSAIDS.
- ❑ <u>*False negative test:*</u> Daily ingestion of vitamin C over 500mg results in false negative test.

<u>Identification of cause</u>

- ❑ Upper and lower GI endoscopy
- ❑ Small bowel follow through
- ❑ Celiac axis and mesenteric angiography

Management
According to the cause.

GASTRIC OUTLET OBSTRUCTION
(Pyloric stenosis)

ETIOLOGY

1. Peptic ulcer in the region of pylorus may lead to gastric outlet obstruction due to:
   - Edema
   - Spasm
   - Fibrous stricture
2. Duodenal ulcer
3. Carcinoma of antrum
4. External compression from carcioma of pancreas.

CLINICAL FEATURES

- Long history of peptic ulcer
- Without symptoms of peptic ulcer, gastric outlet obstruction is likely to have a pyloric carcinoma.
- When the cause is a peptic ulcer, nausea and vomiting become prominent.

Vomiting

- It gives striking relief to the patient
- Vomitus contains food particles which have been eaten even 24 hours or more previously.

Alkalosis

Alkalosis develops if large amount of HCl is lost in vomiting, as occurs particularly in obstruction due to duodenal ulcer.

On Examination

1. *Wasting* due to undernourishment
2. *Dehydration*
3. ***Succussion splash:***
   Succussion splash may be elicited four hours or more after the last meal or drink. While in the normal person splashing occurs for less than an hour after meals because gastric emptying is rapid.
4. *Visible gastric peristalsis* – diagnostic of gastric outlet obstruction.

INVESTIGATIONS

1. **Aspiration of stomach contents:**
   If the volume of aspirated contents is more than 100 ml after fasting overnight, or the aspirate contains food residue, the diagnosis is confirmed.

2. **Barium meal shows:**
   - An increase in the fasting residue of stomach
   - Dilatation of stomach with or without excessive peristalsis.
   - A lesion at or near the pylorus
   - Delayed gastric emptying

3 **Endoscopy** demonstrates the cause & degree of obstruction.

4 **Serum electrolytes show:** depletion of electrolytes

MANAGEMENT

1. **Aspiration**
   - Nothing per oral (NPO)
   - 2 – 4 hourly aspiration for 3-4 days. If volume of aspirate has decreased, fluids by mouth can be allowed.

2. **I/V fluids** for rehydration
3. **Multivitamins**

The majority of patients will be greatly improved by these methods, giving opportunity to complete investigations, and to make the patient fit for subsequent surgery if needed.

CARCINOMA OF THE STOMACH

- It is one of the commonest malignant tumors of the gastrointestinal tract (GIT)
- It is frequent in Japan: may be due to environmental or dietary factors
- Men are more affected than women
- Age: above 50 years.

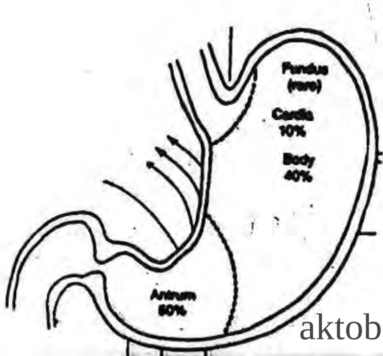
PREDISPOSING FACTORS

1. Chronic gastritis due to Helicobacter pylori infection or autoimmunity.
2. Dietary factors e.g. alcohol, spicy, smoked food & nitrites ingestion. Nitrates are used as preservative in food, they can be converted to the carcinogen nitrosamine by bacteria that colonize the stomach.
3. Diets lacking fresh fruits and vegetables as well as vitamin C and vitamin. A may also contribute.
4. Pernicious anemia
5. Smoking, heavy alcohol intake.
6. Chronic benign gastric ulcers do not develop into malignant ulcers (PK)
7. Partial gastrectomy & gastrojejunostomy; due to intestinal metaplasia in the resected stomach increases the risk of gastric cancer.

PATHOLOGY

Sites:

1. Pylorus and antrum 50– 60% producing gastric outlet obstruction.
2. Body of stomach, often on greater curvature 20 – 30% producing a fungating ulcerating mass.
3. Cardia 20%
4. Fundus 5 – 20%---- producing dysphagia



TYPES:

Intestinal –type adenocarcinoma

It arises from gastric mucus cells that have undergone intestinal metaplasia due to chronic gastritis that may result from Helicobacter pylori infection or autoimmunity associated with pernicious anemia.

Diffuse adenocarcinoma

It arises from the native mucus cells and is not associated with chronic gastritis. It occurs at an earlier age with no male predominance.

SPREAD: By

- Extension through the stomach wall into the peritoneal cavity causing ascites.
- Lymphatics spread: involving lymph nodes around the stomach. Later extension of tumor to involve thoracic duct may lead to involvement of the left supraclavicular lymph node (called **Virchow's node**). Lymph node metastasis is present in about 50% of cases at the time of diagnosis.
- Embolism via portal vein to the liver & hence to the systemic blood stream.

CLINICAL FEATURES

Mostly it is asymptomatic at initial stage & patients usually come at advanced stage of gastric carcinoma.

Symptoms

1. *Epigastric Pain:* It is quite similar to peptic ulcer pain but different in following aspects:
   - It is not relieved by antacids
   - It is not periodic
   - It is not relieved by eating or vomiting
2. *Loss of appetite:* It is the cardinal symptom of gastric cancer.
3. *Weight loss:* due to loss of appetite
4. *Dysphagia* when cancer is near the cardia
5. *Vomiting:* The cancer of pylorus obstructs the gastric outflow and the patient comes with symptoms of pyloric stenosis (vomiting of large quantities of undigested food, epigastric discomfort and distension).

Signs

- Wasting and pallor
- Palpable left supraclavicular lymph node (Virchow's node) due to secondary deposits – presence of Virchow's node is termed as Troisier's sign
- Epigastric tenderness
- Palpable epigastric mass
- Metastasis:
  Peritoneal metastasis produce ascites
  Liver metastasis produces jaundice & hepatomegaly.

INVESTIGATIONS

1. **Gastroscopy & biopsy**
2. **Barium meal** – shows filling defect or an irregular ulcer with rolled edges.
3. **CT and ultrasound:** CT shows gastric wall thickening. Ultrasound demonstrates masses and wall thickening. Liver secondaries can be detected. Endoscopic ultrasound can demonstrates penetration of cancer through gastric wall.

MANAGEMENT

Surgery

Surgical resection is a curative treatment for early gastric cancer but most of the cases are found to be inoperable at the time of surgery. Post- operative radiotherapy is ineffective and adjuvant chemotherapy following surgery have been disappointing.

Palliative measures

Palliative measures are usually performed to prevent obstruction and to relieve the patient's immediate symptoms such as endoscopic laser ablation of tissue to control dysphagia. Carcinoma at cardia may require endoscopic dilatation, laser therapy or insertion of metalic stent to allow adequate swallowing.

Nutrition

Improve nutrition if necessary by parenteral or enteral feeding. Fluid electrolyte imbalance and anemia should be corrected.

PROGNOSIS

- Overall five-year survival rate is 10%.
- Five year survival rate after resection is only 20%

GASTRIC LYMPHOMA

- Gastric lymphoma may be primary (arising from gastric mucosa) or may present as a site of secondary involvement in patients with nodal lymphoma. Following discussion is confined to primary gastric lymphoma, while secondary gastric lymphoma is discussed in the section of blood disorders.
- More than 95% of primary gastric lymphoma are non- Hodgkin's B cell lymphomas arising from mucosa associated lymphoid tissue (MALT).
- Peak age is sixth decade.
- Infection with Helicobactor pylori may be an important risk factor.
- Presentation may be abdominal pain, weight loss or bleeding. Night sweats are absent in primary lymphoma (usually present in secondary).
- It is usually localized to stomach wall or adjacent lymph nodes and has an excellent prognosis. Complete regression of lymphoma may occur after eradication of H. pylori infection.
- *Investigations:* endoscopic biopsy, endoscopic ultrasound. For staging CT abdomen and chest.
- *Treatment* is surgical with postoperative radiotherapy and chemotherapy.
- *Prognosis* is good, with 85% five-year survival in stage I and 35-65% in stage II.

MALABSORPTION

The inadequate transport of one or more of the constituents of the normal diet from the intestinal lumen across the intestinal epithelium into the portal circulation is called malabsorption.

SITES OF NUTRIENT ABSORPTION

The sites of nutrient, vitamin and mineral absorption are the following:

Duodenum: iron, calcium, magnesium, folic acid, water soluble vitamins, amino acids, monosacchrides.

Jejunum: fatty acids, amino acids, monosacchrides, and water-soluble vitamins.

Ileum: monosacchrides, fatty acids, amino acids, fat soluble vitamins (A, D, E, K), vitamin B12 and conjugated bile salts.

PHYSIOLOGY OF NUTRIENT ABSORPTION

There are three phases of normal absorption;

- **Luminal phase:** characterized by hydrolysis and solubilization of nutrients.
- **Mucosal phase**: consists of further breakdown of nutrients and transfer into the cell.
- **Transport phase:** consists of removal of nutrients into vascular or lymphatic circulation.

INTRALUMINAL PHASE (Digestive phase)

- Dietary fats, proteins, and carbohydrates are hydrolyzed and solubilized by pancreatic and biliary secretions.
- Fats are broken down by pancreatic lipase to monoglycerides and fatty acids that form misclles with bile salts. Miscelles are important for the solbilization and absorption of fats soluble vitamins (A, D, E, K).
- Proteins are hydrolyzed by pancreatic proteases to di- and tripeptides and amino acids.
- Carbohydrates are degraded into oligosaccharides and disaccharides by the pancreatic amylase.
- Pancreatic insufficiency may be due to chronic pancreatitis, cystic fibrosis, pancreatic cancer and Zollinger-Ellison syndrome leading to malabsorption.
- Decreased bile salt concentrations may be due to biliary obstruction, cholestatic liver disease, bacterial over growth leading to bile salts deconjugation or decreased reabsorption due to ileal disease such as Crohn's disease.

MUCOSAL PHASE

Mucosal impairment is the most common cause of malabsorption. The mucosal phase requires a sufficient surface area of intact small intestinal epithelium. Brush border enzymes are important in the hydrolysis of disaccharides and di- and tripeptides. Malabsorption of specific nutrients may occur as a result of deficiency in an isolated brush border enzyme such as lactase deficiency. Mucosa may be impaired due to diseases of small intestine such as celiac disease or Crohn's disease.

TRANSPORT PHASE PHASE

After absorption, nutrients leave the cells through the vascular or lymphatic circulation requires intact lymphatic system. Obstruction of lymphatics results in impaired absorption of chylomicrons and lipoproteins , resulting in steatorrhea.

CLASSIFICATION OF MALABSORPTIVE DISORDERS

DISORDERS OF INTRALUMINAL DIGESTION

Pancreatic insufficiency

- Chronic pancreatitis
- Cystic fibrosis
- Carcinoma of the pancreas

Deficiency of bile acids

- Interruption of the enterohepatic circulation of bile acids due to resection or disease of the terminal ileum.
- Colonization of the small intestine with bacteria which deconjugate bile acids, which reduces their efficiency (stagnant loop syndrome).

Uncoordinated gastric emptying

It delivers gastric chyme too quickly to the intestine

- Gastroenterostomy
- Partial gastrectomy

DISORDERS OF MUCOSAL PHASE

Generalized mucosal abnormalities.
The mucosa is abnormal histologically

- Coeliac disease
- Tuberculosis
- Tropical sprue
- Lymphoma
- Radiation enteritis
- Whipple's disease

Malabsorption of specific substances
The mucosa is normal histologically
Lactase deficiency

DISORDERS OF TRANSPORT PHASE

- Vascular: vasculitis, atherosclerosis
- Lymphatic: lymphanggiectasia, infiltrations

CLINICAL FEATURES

1. Diarrhea, steatorrhoea, abdominal pain, distension & loss of weight
2. Specific nutritional deficiencies such as iron, folic acid, B12, Vit. K, calcium, vitamin D deficiency, multivitamin and albumin deficiency.

Nutrient	Results of malabsorption
Fats	Steatorrhoea, weight loss
Carbohydrates	Flatulent dyspepsia, abdominal distension
Protein	Wasting, edema
Folic acid	• Macrocytic, megaloblastic anemia • Glossitis
Vitamin B12	• Macrocytic, megaloblastic anemia • Glossitis • Mental and neurological disturbances
Vitamin B complex	dermatitis, polyneuritis
Vitamin C	Bleeding tendency
Vitamin A	• Follicular hyperkeratosis • Xerophthalmia
Vitamin D & calcium	Osteomalacia, tetany
Vitamin K	Purpura, haemorrhages
Iron	Anemia
Sodium	Muscular weakness, cramps
Potassium	Flaccidity, arrhythmias
Magnesium	Muscular weakness

INVESTIGATIONS

There is a long list of investigations for malabsorption, therefore clinical assessment is very important to perform investigations that are really helpful in diagnosis and management.

FECAL FAT ANALYSIS

Identification of steatorrhea (fat in stool) is essential in any assessment of maldigestion or malabsorption.
Following two methods are easy to confirm steatorrhea.

- **Sudan III- stained stool smear:** it is the microscopic examination of Sudan- stained stool smear that detects fat in stool.

- **Quantitative fecal fat:** It is more sensitive test to confirm steatorrhea. Stool is collected for three consecutive days while the patient is on a diet containing 80-100 g fat per day, and specimen is then analyzed for fat content. Fat excretion more than 6 g/day confirms fat malabsoption (steatorrhea). However this test does not indicate the cause of steatorrhea.

XYLOSE ABSORPTION- EXCRETION TEST

- When fat malabsorption is demonstrated by quantitative fecal fat test (fat >6gm/24hours), a xylose- absorption- excretion test is performed next.
- Patient ingests 25 g of D-xylose and urine is collected for the next 5 hours. Healthy subjects excrete more than 4.5 g of D-xylose in 5 hours.

This test reflects the permeability and surface area of mucosa and serves as an indicator of mucosal integrity.

A normal xylose test rules out diffuse mucosal disease and suggests that the patient's disorder is digestive such as *pancreatic or bile salt deficiency*. Then specific tests for pancreatic insufficiency and bile salts deficiency are performed.

SMALL INTESTINAL BIOPSY

Biopsies are obtained via an endoscope passed into the duodenum using large forceps. A smear of jejunal juice or mucosal impression is helpful to diagnose Giardia intestinalis.

Biopsy has diagnostic value (diffuse lesions)

- Whipple's disease
- Abetalipoproteinemia
- Agammaglobinemia

Biopsy may have diagnostic value (patchy lesions)

- Intestinal lymphoma
- Lymphangiectasia
- Amyloidosis
- Crohn's disease
- Parasitic infestation

Biopsy is abnormal but not diagnostic

- Celiac disease
- Tropical sprue
- B12, folic acid deficiency
- Scleroderma
- Bacterial over growth

SMALL BOWL FOLLOW- THROUGH

Barium studies are helpful in the presence of gross anatomical defects such as diverticula, strictures, lymphoma and Crohn's disease. Dilatation of folds and a changed fold pattern may suggest malabsorption.

X-RAY ABDOMEN AND CHEST

Plain X-ray • abdomen may show pancreatic calcification due to chronic pancreatitis and chest X-ray may demonstrate pulmonary tuberculosis as a cause of malabsorption.

HYDROGEN BREATH TEST

This test is based on the principle that bacterial degradation of luminal compounds causes the release of gases that can be measured in breath. In the presence of bacterial overgrowth, orally ingested glucose ferments in the small bowel (instead of being absorbed) which results in increased breath hydrogen.

SMALL INTESTINAL BIOPSY IN MALABSORPTION

- **Celiac disease:** subtotal villous atrophy, crypt hyperplasia with chronic inflammatory cells in lamina propria.
- **Tropical sprue**: partial villous atrophy of jejunal mucosa.
- **Whipple's disease**: subtotal villous atrophy containing periodic acid – Schiff (PAS)- positive macrophages.
- **Giardiasis**: villous atrophy and prence of organism.
- **Intestinal lymphangiectasia:** dilatation of lymphatics with low serum circulating lymphocytes (lymphopenia)

VITAMIN B12 ABSORPTION TEST (SCHILLING TEST)

Principle

Absorption of vitamin B12 requires several steps as following:

- B12 binds to R protein in saliva.
- In the duodenum, pancreatic proteases hydrolyze the R protein, allowing vitamin B12 to bind with intrinsic factor released by the gastric parietal cells.
- Vitamin B12 and intrinsic factor complex is then absorbed by specific receptors found on enterocytes in the distal ileum.
- Therefore malabsorption may be due to pancreatic disease, lack of intrinsic factor, bacterial overgrowth (as gram negative bacteria take B12) or ileal disease.

Procedure

Phase I

- Intramuscular injection of vitamin B12 1mg is given to saturate hepatic storage.
- The patient ingests radiolabeled vitamin B12, and urine is collected for 24 hours. Normal

subjects excrete more than 10% of the radioactive dose.

Phase II

If the above test is abnormal, the test is repeated while the patient is given B12 and intrinsic factor.

Result

- If excretion is now normal, pernicious anemia is the diagnosis.
- If excretion still abnormal, lesion is in the terminal ileum or there is bacterial overgrowth.

Phase III

Give antibiotics for bacterial overgrowth, if excretion is still abnormal, an ileal disease is diagnosed.

DIAGNOSTIC APPROACH

HISTORY

Ask about symptoms such as diarrhea, steatorrhea, abdominal pain, weight loss and bone pain

EXAMINATION

Look for the evidence of nutrient deficiencies (signs) such as anemia, generalized wasting, bruises, glossitis, neuropathy and pedal edema.

INVESTIGATIONS

Because of large number of available diagnostic tests, a rational use of these tests is necessary in evaluation the patient with suspected malabsorption.

Investigations to confirm malabsorption

- Blood CP shows anemia:
  - Low MCV: iron deficiency
  - High MCV: folic acid or B12 deficiency
- Serum albumin-- low
- Serum calcium --low
- PT-- high
- Serum cholesterol --low

Investigations to identify the cause

72-hours fecal fat measurement

- ***Normal:*** evaluate for other causes of chronic diarrhea.
- ***Abnormal:*** D-xylose test and small bowel follow through

D-xylose test

- *Normal:* suggests pancreatic deficiency. Perform tests for pancreatic functions such as
  - Stool and serum pancreatic enzymes
  - X-ray abdomen, ultrasound and CT abdomen, ERCP.
- ***Abnormal:*** suggests bacterial overgrowth or mucosal disease.

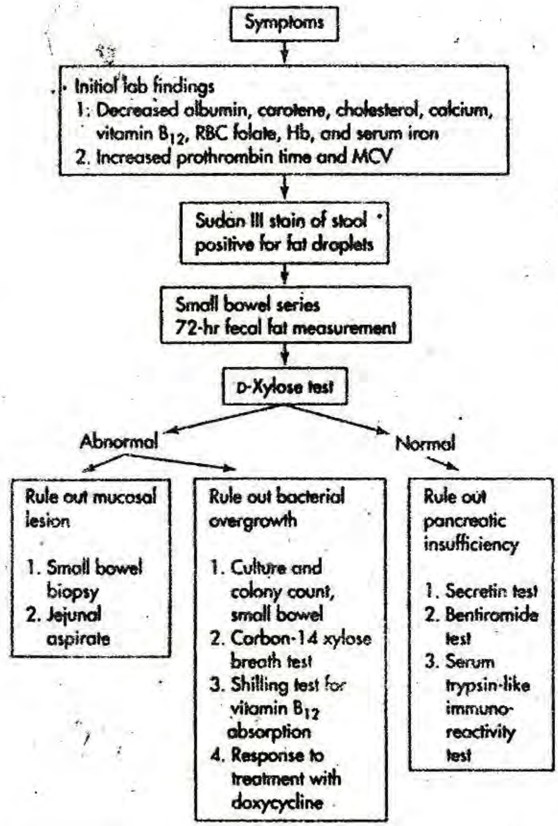
Perform tests for bacterial growth such as:

- Hydrogen breath test
- Carbon-14 xylose breath test
- Culture of jejunal aspirate.

Perform tests for mucosal disease such as:

Small intestinal biopsy

- Normal villi—suggests parasitic infestation or pancreatic disease.
- Abnormal villi: may be of two types:
  - *Subtotal villous atrophy*: Celiac disease, dermatitis herpatiform, Zollinger- Ellison syndrome.
  - *Partial villous atrophy:* Tropical sprue, Giardiasis.



Diagnostic approach to malabsorption.

CELIAC DISEASE

Celiac disease (gluten-sensitive enteropathy) is characterized by intestinal mucosal injury resulting from immunologic intolerance to gluten in persons genetically predisposed to this condition. In Celiac disease there is an abnormal jejunal mucosa that improves morphologically when the patient is treated with a gluten free diet and relapses when gluten is reintroduced.

- Gluten is contained in the cereals, wheat, rye & barley.

INCIDENCE

- Common in Europe 1 in 2000
- Occurs throughout the world
- Rare in black Africans
- Age – any age group, children between 6month and 24months after introduction of weaning food. About half cases in childhood and adulthood.
- Sex – Mostly females
- 10-15% of first degree relatives are also affected

INHERITANCE

There is an increased incidence of Celiac disease within families, showing high association with the histocompatibility antigens B6, DR3, DR7, and DQ2.

PATHOGENESIS

Mucosa of small intestine is found abnormal, induced by a gliadin component of gluten protein. Local immunological response to gliadin is responsible for the damage to the mucosa. Antibodies to gliadin are found in the peripheral blood.

Normal mucosa of small intestine has finger like villi normally, but in Celiac disease there is absence of villi as seen under microscope, called subtotal villous atrophy. There are certain other conditions that cause subtotal villous atrophy and Celiac disease is differentiated from them on clinical features.

Clinical features

Children: mostly under 2 years old and within 6 months of starting cereals

- Child becomes irritable
- Stools become voluminous & pale
- Abdominal distension
- Anemia & growth retardation in late stages.

Adults: Less commonly the disorder may manifest for the first time in adult life with following symptoms of malabsorptive state:

- Diarrhea, weight loss, anemia
- Peripheral neuropathy
- Vitamin deficiency
- Hypoproteinemia, edema, bone pain

Identify other autoimmune diseases when one autoimmune disease is present (as associated with Celiac disease). These autoimmune disorders may be thyroid disease, insulin dependent diabetes, inflammatory bowel disease, chronic liver disease and fibrosing allergic alveolitis.

INVESTIGATIONS

Routine lab tests
Blood CP, serum ferritin, red cell folate, serum vitamin B12 level, serum calcium, alkaline phosphatase, albumin and prothrombin should be performed in all patients with suspected malabsorption.

Antigliadin antibodies
IgG and IgA antigliadin antibodies are present in > 90% of cases; IgG is more sensitive and IgA is more specific.
IgA endomysial antibody test has sensitivity and specificity more than 90% but use of this test is limited by cost and variability of results from different labs.
Tissue transglutaminase antibodies have sensitivity and specificity more than 95%.

- Tests for antibodies are negative after 6-12 months of dietary gluten withdrawal.
- Antigliadin antibody test is mostly performed due to availability and cost.

Jejunal biopsy
Endoscopic mucosal biopsy of distal duodenum or proximal jejunum is the standard method for confirmation of diagnosis in patients with positive serologic (antibody) test for Celiac disease.

The histologic pattern is subtotal or total villous atrophy, hypertrophy of intestinal crypts, and extensive infiltration of lamina propria with lymphocytes and plasma cells.

Other conditions that mimic Celiac disease on histology given in the box on next column.

IMPORTANT CAUSES OF SUBTOTAL VILLOUS ATROPHY
- Celiac disease
- Tropical sprue
- Dermatitis herpatiformis
- Lymphoma
- AIDS enteropathy
- Giardiasis
- Hypogammaglobinemia
- Radiation
- Whipple's disease
- Zollinger – Ellison syndrome

Small bowel follow through
It shows dilatation of small bowel, thick or diminished folds and sometimes flocculation of contrast.

Hematological tests
- Anemia of iron deficiency (microcytic) or folic acid deficiency (macrocytic) or combined is often present. B12 deficiency is rare.
- Hypersegmented polymorphonuclear leukocytes and Howell- Jolly bodies (due to splenic atrophy) are present on blood film.

COMPLICATIONS
- Intestinal T cell lymphoma
- Carcinoma of small intestine or esophagus
- Ulcerative jejunitis (fever, abdominal pain, perforation and bleeding). Diagnosis through barium studies or laparotomy. Steroids and immunosuppresive drugs such as azathioprine are used for treatment.
- Complications of nutritional deficiencies such as metabolic bone disease due to calcium and vitamin- D deficiency.

MANAGEMENT
- Strictly gluten free diet. Despite advice many patients do not keep to a strict diet and do not maintain good health. Give a food chart to the patient having clear instructions what they should avoid.
- Rice, maize and potatoes can be taken instead of wheat, rye, barley (*Joe*) and oats.
- Minerals & vitamins supplements
- Clinical response may be seen within a few weeks.

- Patients should have pneumococcal vaccination every five year because there is *splenic atrophy.*
- Patient with refractory sprue may respond to corticostaroids, azathioprine, or cyclosporine.

DERMATITIS HERPETIFORMIS

Dermatitis herpatiformis is regarded as a cutaneous variant of Celiac disease. This is an uncommon blistering itchy eruption over extensor surfaces of limbs and back, scalp and neck. It occurs in less than 10% of patients with Celiac disease; however almost all patients who present with dermatitis herpatiformis have evidence of Celiac disease on intestinal biopsy, though it may not clinically evident.

The inheritance and immunological abnormalities are same as for Celiac disease. The skin eruptions respond to dapsone but both the gut and the skin will improve on a gluten- free diet.

TROPICAL SPRUE

Tropical sprue is the malabsorption occurring in a patient resident or visitor to a tropical area, in the absence of other intestinal disease or parasites. (The term tropical sprue is reserved for severe malabsorption of two or more substances that is usually accompanied by diarrhea and malnutrition).

ETIOLOGY

- Exact cause unknown
- Likely to be infection responsible for this

CLINICAL FEATURES

1. Abdominal distension, diarrhea, weight loss and anorexia
2. Epidemics can break out in villages affecting thousands of people at the same time
3. In chromic case, features of malnutrition are obvious e.g. edema due to hypoalbuminemia, glossitis and stomatitis due to vitamins deficiency.

DIAGNOSIS

1. Acute infective causes of diarrhea must be excluded particularly Giardia
2. Malabsorption should be demonstrated. particularly fat & vit B12 malabsorption.
3. Jejunal mucosa shows partial villous atrophy.

MANAGEMENT

1. Dehydration and electrolyte deficiencies must be corrected in severe diarrhea
2. Tetracycline or oxytetracycline 250 mg 1 cap – 6 hourly for 28 days
3. Folic acid 5 mg daily – Initially 10-20 mg daily for 14 days.
4. Iron & B-complex supplements

BACTERIAL OVERGROWTH

(Blind loop Syndrome)

This syndrome is characterized by intestinal abnormality associated with overgrowth in the small intestine and causing steatorrhoea and Vit B12 malabsorption.

ETIOLOGY

- In normal person, the upper part of small intestine is almost sterile, containing few organisms derived from the mouth. Gastric acid kills most organisms and intestinal motility keeps the jejunum empty.

- Bacterial proliferation occurs due to impairment of these physiological processes. Bacterial proliferation is also predisposed to by structural abnormalities which deliver colonic bacteria to the small intestine e.g. fistulas, impaired intestinal motility.

- Organisms are E. coli and Bacteroides more than 10^6 /ml of aspirate from upper jejunum. These bacteria deconjugate bile salts. Steatorrhoea occurs as a result of conjugated bile salts deficiency.
- The bacteria also utilize B12, leading to B12 deficiency.

Causes of small bowel bacterial overgrowth	
Mechanism	**Examples**
Hypo- or achlorhydria	Pernicious anaemia Partial gastrectomy Long-term proton pump inhibitor therapy
Impaired intestinal motility	Scleroderma Diabetic autonomic neuropathy Chronic intestinal pseudo-obstruction
Structural abnormalities	Gastric surgery (blind loop after Billroth II operation) Jejunal diverticulosis Enterocolic fistulae (e.g. Crohn's disease) Extensive small bowel resection Strictures (e.g. Crohn's disease)
Impaired immune function	Hypogammaglobulinaemia

CLINICAL FEATURES

- Diarrhea and/or steatorrhoea
- Anemia due to vit B12 deficiency

Management

- Tetracycline 250 mg 1 cap 6 hourly for 7 days is the treatment of choice.
- Metronidazole (Flagyl) 400 mg 8 hourly or ciprofloxacin (Ciproxin) 250mg 12 hourly are alternatives.
- Intramuscular vitamin B12 is needed in chronic cases.

INTESTINAL RESECTION

(Short Gut Syndrome)

Resection of small intestine, sometimes extensive may be necessary in Crohn's disease and in vascular insufficiency with gangrene. The consequence of small intestinal resection depends on extent & site of resection.

Extent: 30-50% resection can be tolerated without undue problems.

CAUSES OF SHORT GUT SYNDROME

Adults
- Crohn's disease
- Mesenteric infarction
- Radiation enteritis
- Volvulus

Children
- Necrotizing enterocolitis
- Congenital anomalies

Site of resection

The ileum has specific receptors for the absorption of bile salts and vit B12, so that resections will lead to malabsorption of these substances resulting in:

- *Diarrhea*: Bile salts cannot be absorbed and enter the colon where they interfere with water and electrolyte absorption, causing diarrhea.
- *Steatorrhoea*: Bile salts become deficient in upper small intestine because of their loss in stool, fat malabsorption occurs with fatty diarrhea.
- *Gallstone*: Super- saturated bile because of diminished bile acid pool results in gallstone formation.
- *Oxalate nephrolithiasis:* Increased oxalate absorption is caused by the presence of bile salts in the colon. This gives rise to renal oxalate stones.

MANAGEMENT

1. Parenteral fluids and feeding is necessary initially in post-operative period, giving time for intestinal adaptation to take place
2. Loperamide (Imodium) 2 mg initially 2 caps, then 1 at each loose stool.
3. Cimitidine (Tagamet) 400mg B.D to reduce volume of gastric secretion.
4. Cholestyramine orally at meal time acts to bind bile acids in colon, thus preventing diarrhea.

PARASITE INFESTATION

GIARDIASIS

Giardia lamblia not only produces diarrhea but can also produce malabsorption and steatorrhoea due to partial villous atrophy.

CLINICAL FEATURES

- Diarrhea, abdominal pain, anorexia, nausea, vomiting.
- May be abdominal distension and tenderness.

DIAGNOSIS:

(a) Three specimens of stool are collected at 2-3 days interval and examined for cysts within an hour of collections.
(b) Duodenal fluid aspiration or jejunal biopsy during endoscopy shows Giardia lamblia.

MANAGEMENT

- Tab. Tinidazol (Fasigyn 500 mg) initially 4 tabs as a single dose then 2tabs daily for 5-7 days.
- Tab. Metronidazole (Flagyl 400 mg) 3 times daily for 5 days.

WHIPPLE 'S DISEASE

This rare condition is characterized by infiltration of intestinal mucosa and other organs with macrophages which stain positive with periodic acid-Schiff (PAS) reagent.

This is a multisystem disease that can involve any organ, sometimes before GI involvement is apparent.

On electron microscopy, gram- positive bacilli (Tropheryma whippelli) can be seen within the macrophages. Villi are flattened and densely packed macrophages occur in lamina propria. These macrophages may obstruct lymphatics, causing fat malabsorption (steatorrhea).

- ❑ Whipple's disease is a very favorite question for MCQs in all exams.

CLINICAL FEATURES

- Middle aged men are most commonly affected.
- Arthralgia or a migratory nondeforming arthritis occur in 80% and are typically the first symptom experienced.
- GI symptoms occur in 75% of cases and include abdominal pain, rhea, malabsorption, abdominal distensi.. and weight loss. Protein losing enteropathy may lead to hypoalbuminemia and edema.
- Other features are intermittent fever, chronic cough, generalized lymphadenopathy, CCF or valvular disease, uveitis, dementia, seizures, opthalmoplagia.
- Examination may reveal hypotension, fever, features of malabsorption, lymphadenopathy, heart murmurs, swelling of peripheral joints, edema and *hyperpigmentation* on sun-exposed areas in up to 40% of cases.

CLINICAL FEATURES OF WHIPPLE'S DISASE

1. **GIT**:
   Diarrhea, steatorrhea, weight loss, bloating, protein losing enteropathy, ascites, hepatosplenomegaly.
2. **Musculoskeletal**:
   Seronegative large joint arthropathy, sacroiliitis.
3. **Cardiac**:
   Pericarditis, myocarditis, endocarditis, coronary arteritis
4. **CNS:**
   Apathy, dementia, myoclonus, meningitis, cranial nerve palsy.
5. **Pulmonary:**
   Chronic cough, pleurisy, pulmonary infiltrate.
6. **Blood:**
   Anemia, lymphadenopathy.
7. **Other**: fever, pigmentation.

Differential Diagnosis

Whipple's disease should be suspected in patients who present with signs of malabsorption, fever of unknown origin, lymphadenopthy, seronegative arthritis or culture – negative endocarditis. Small bowl biopsy is diagnostic. Other conditions that mimic Whipple's disease are sarcoidosis, Reiter's syndrome, vasculitis, Bachet's disease, intestinal lymphoma and subacute endocarditis.

Management

Co-trimoxazole (Septran DS) one tab twice daily for one year is the treatment of choice. If patient is allergic to Septran then chloramphenicol or ceftriaxone are alternatives.

PROTEIN -LOSING ENTEROPATHY

Protein – losing enteropathy is characterized by excessive loss of protein into the gut lumen, resulting in hypoproteinemia. This protein loss is more common in ulcerative lesions of the gut. Patient presents with peripheral edema and hypoproteinemia in the presence of normal liver function and without proteinuria. There may be the features of underlying cause.

CAUSES OF PROTEIN- LOSING ENTEROPATHY.

With mucosal erosions or ulcerations
- Crohn's disease
- Ulcerative colitis
- GI malignancy
- Lymphoma
- Radiation damage
- Intestinal tuberculosis

Without mucosal erosions or ulcerations
- Menetrier's disease
- Bacterial overgrowth
- Celiac disease
- Tropical sprue
- Eosinphilic gastroenteritis
- SLE

With lymphatic obstruction
- Intestinal lymphangiectasia
- Constrictive pericarditis
- Lymphoma
- Whipple's disease

INTESTINAL ISCHEMIA

Intestinal ischemia results from occlusion of arterial inflow, venous outflow or failure of perfusion resulting in abdominal pain called abdominal angina.

❑ This is an important question for MCQs.

CAUSES OF INTESTINAL ISCHEMIA

Arterial inflow occlusion
- Atheroma
- Thrombosis
- Embolus
- Aortic disease
- Vasculitis e.g Takayasu's arteritis
- Tumor (causing compression of vessel)

Venous outflow occlusion (Mesenteric vein occlusion)
- Hypercoaguable states e.g malignancy, protein C, protein S, or antithrombin III deficiency).
- Antiphophlipid antibody
- Intra- abdominal sepsis
- Portal hypertension and cirrhosis

Failure of perfusion
- Hypotension. shock

Acute small intestinal ischemia

- An embolus from heart in patient with atrial fibrillation is the commonest cause, usually occluding the superior mesenteric artery.
- Patient presents with sudden abdominal pain and vomiting. Abdomen is usually distended, tender and bowel sounds are absent. Patient is hypotensive and ill looking.
- Angiography may be performed in a stable patient and thrombolytic therapy (altepase) may be given for thrombotic disease.
- For unstable patient treatment is usually laparotomy with thromboembolectomy and resection of gangrenous bowel. Antibiotics are given to all patients. Mortality is high.

Chronic small intestinal ischemia

- This is due to atheromatous occlusion or cholesterol emboli of the mesenteric artery, particularly in elderly.
- Patient presents with abdominal pain occurring after food. Acute mesenteric occlusion may develop on chronic occlusion.
- Diagnosis is made with angiography.

Mesenteric vein occlusion

Diagnosis is made with contrast CT or angiography. Treatment is long term anticoagulation. Surgery is reserved for bowel infarction.

Ischemic colitis

- Occlusion of branches of superior or inferior mesenteric arteries often in older age group commonly presents with sudden onset of abdominal pain and passage of bright red blood per rectum with or without diarrhea. In majority of cases splenic flexure and left colon are affected. Underlying cardiovascular disease may be evident.
- On examination abdomen is distended and tender.
- Abdominal x- ray often shows thumb printing at the site of splenic flexure.
- Medical symptomatic management is usually adequate; surgery may be required for perforation, gangrene or stricture formation.

TUMORS OF SMALL INTESTINE

INTESTINAL LYMPHOMA

Gastrointestinal lymphomas may arise in the GI tract (primary lymphoma) or involve secondarily with disseminated disease (secondary lymphoma). Primary lymphomas occur most commonly in the distal small intestine. The majority are non- Hodgkin's high – grade B cell lymphoma (T cell lymphoma in Celiac disease). Primary intestinal lymphoma accounts for about 20% of small bowel malignancy.

Clinical features

- Abdominal pain due to development of localized or nodular masses that narrow the intestinal lumen resulting in periumblical pain (made worse by eating), weight loss, nausea, vomiting, abdominal distension, intestinal obstruction anemia and occult blood in stool. Protein losing enteropathy may result in hypoalbuminemia.
- Clinically there is no palpable lymphadenopathy, or hepatosplenomegaly.

  There is no evidence of lymphoma on chest X-ray or CT scan, peripheral blood film, bone marrow aspiration and bone marrow biopsy.

Diagnosis

- Barium study may help in localize the site of lesion by showing thickening of mucosal folds, mucosal nodules, areas of irregular ulceration, or stasis of contrast material.
- Diagnosis requires endoscopic or laproscopic biopsy. For staging CT abdomen and chest is required.

Treatment

Treatment depends on stage of disease. Resection is recommended if feasible. Even in late stages surgical debulking may improve survival. Chemotherapy and radiotherapy are advised for disseminated disease and after surgery.

CARCINOID TUMORS

- Carcinoid tumors originate from enterochromaffin cells (APUD cells) of the intestine and are 10% of small bowel tumors.
- They secrete serotonin or its precursors.
- The most common sites are terminal ileum, appendix and the rectum.
- Clinically most carcinoid tumors are asymptomatic until metastases are present.
- Rectal carcinoids less than 1cm and appendical carcinoids less than 2cm never metastasize. Tumors more than 2cm metastasize in 20% cases of appendical and 10% cases in rectal carcinoids.
- Tumors of appendix may present as acute appendicitis.
- Biochemical abnormalities: the tumors secrete serotonin, bradykinin, histamine and prostaglandins that produce clinical features.

Carcinoid syndrome

Carcinoid syndrome occurs in only 5% of patients with carcinoid tumors and only when there is liver metastasis.

- This syndrome manifests as spontaneous bluish-red flushing, predominantly on the face and neck. This can lead to permanent changes with telangiectasis.
- Gastrointestinal symptoms consist of abdominal pain and recurrent diarrhea.
- Cardiac manifestations are found in 50% of patients and consist of *pulmonary stenosis* or *tricuspid regurgitation*. Examination of abdomen shows hepatomegaly.

Investigations

- Elevated levels of serotonin metabolite 5- hydroxyindoleacetic acid (5-HIAA) in 24 - hours urinary collection > 10mg.
- Elevated serum serotonin.
- Ultrasound abdomen to confirm liver metastases.
- Somatoststin receptor scintigraphy is positive in more than 90% of cases with metastatic carcinoid.

Treatment

- Surgical resection of tumor if no metastases.
- Palliative treatment of carcinoid syndrome with octreotide 200 microgram 8-hourly subcutaneously inhibits serotonin secretion producing relief from carcinoid syndrome.
- Resection of hepatic metastasis may provide dramatic improvement in patient with carcinoid syndrome.
- Hepatic artery occlusion and chemotherapy may provide symptomatic relief in some patients with hepatic metastasis.

CLINICAL FEATURES OF CARCINOID SYNDROME

- Small bowel obstruction due to tumor mass.
- Intestinal ischemia due to mesenteric infiltration or vasospasm.
- Hepatic metastasis causing pain, hepatomegaly, and jaundice.
- Flushing and wheezing.
- Diarrhea
- Cardiac involvement causing tricuspid regurgitation, pulmonary stenosis leading to heart failure.
- Facial telangiectasia

ABDOMINAL TUBERCULOSIS (Abdominal Kock's)

Mycobacterium tuberculosis can affect the intestine peritoneum, mesenteric lymph nodes and liver.

PERITONEAL TUBERCULOSIS

Tuberculous peritonitis follows either the direct spread of tubercle bacilli from ruptured lymph nodes and intra-abdominal organs or hematogenous seeding. It is believed that lymphatic spread from an intestinal focus may lead to peritoneal involvement.

TIPS: This is a major topic of discussion in long and short cases if you get patient with ascites.

Clinical features

- Patient presents with nonspecific abdominal pain, low - grade fever, anorexia, weight loss and ascites. About half of the patients have underlying cirrhosis; therefore diagnosis may be delayed due to predominant features of liver disease. A high index of suspicion is required for prompt diagnosis and treatment.
- On palpation abdomen may be rigid (Doughy abdomen) if there is underlying peritonitis; abdomen is distended if ascites is present.
- The fibroplastic bands and adhesions between intestinal coils sometimes obstruct the bowel and produce features of *subacute intestinal obstruction.*

INVESTIGATIONS

Chest x-ray

Chest x-rays are abnormal in over 70%, but active tuberculous pulmonary disease is evident in less than one- fourth of patients.

Ascitic fluid analysis

Ascitic fluid is exudate with:

- Total protein >2.5 g/dl.
- LDH >90 units/lit
- WBC >500/µL with lymphocytes predominant

Ascitic fluid PCR

It is a new and sensitive test that detects DNA of mycobacterium tuberculosis.

Ascitic fluid acid -fast bacilli (AFB)

Smears of ascitic fluid for acid-fast bacilli are rarely positive.

Ascitic fluid AFB culture

AFB culture is positive in 20% of cases.

Laproscpic peritoneal biopsy

Laproscopy is the definitive means of establishin_ the diagnosis. In over 90% of patients characteristic peritoneal nodules are visible at laproscopy and granulomas can be documented on peritoneal biopsy. Peritoneal culture requires 4-6 weeks and is positive in less than two-third of patients.

INTESTINAL TUBERCULOSIS

Types:

- Secondary intestinal tuberculosis is the commonest complication of pulmonary tuberculosis and results from infection with mycobacterium tuberculosis.
- Primary intestinal tuberculosis occurs due to ingestion of milk containing bovine strain of tubercle bacilli.

SECONDARY INTESTINAL TUBERCULOUS

This form of tuberculosis occurs as a result of swallowing of infected sputum by patient with active pulmonary tuberculosis or reactivation of a dormant intestinal focus, usually in the terminal ileum or cecum. Intestinal tuberculosis may cause mucosal ulcerations or scarring and fibrosis with narrowing of the lumen.

Pathologically intestinal tuberculosis may be ulcerative(60%) or hypertrophic type (10%).

In ulcerative type multiple superficial ulcers are largely confined to epithelial surface and the long axis of ulcer is perpendicular to the long axis of GI segment and hence it is prone for stricture formation.

Hypertrophic lesion is common in ileocecal region consisting of scarring, fibrosis, heaped up mass mimicking carcinoma and palpable as a thickened and bulky mass.

SYMPTOMS

Patient presents with chronic abdominal pain, obstructive symptoms, weight loss, fever and diarrhea.

Abdominal pain: chief complaint

- Site: most often right lower quadrant but may be felt in periumbilical region or hypogastrium.
- Character: Cramping or dull, when there is partial intestinal obstruction severe cramps develop.
- Aggravating factor: Eating

Diarrhea

Daily 3-6 semisolid to liquid stools, mucus may be present but blood & pus are rare.

Weight loss:

It results from anorexia and fear of eating (sitophobia) because pain increases after meals.

Non-specific features of tuberculosis e.g. anorexia, fever, sweating etc.

SIGNS

1. Vigorous peristaltic activity or distended bowel may be noted.
2. Tenderness usually in right lower quadrant
3. Muscle guarding if peritoneum is involved **(Doughy abdomen)**
4. Tender fixed mass palpable in right iliac fossa in case of ileocecal tuberculosis

DIFFERENTIAL DIAGNOSIS

Differential diagnosis of palpable lump in right iliac fossa includes

1. Crohn's disease
2. Intestinal amebiasis
3. Intestinal lymphoma
4. Carcinoma of colon
5. Ileocecal tuberculosis

DIAGNOSIS

1. **Clinical:** Such as abdominal signs and symptoms in a patient with pulmonary tuberculosis.
2. **Barium meal:** may demonstrate mucosal ulcerations, thickening, or stricture formation.
3. **Ultrasound abdomen:** may show mesenteric thickening and lymph node enlargement.
4. **Biopsy:** Specimen obtained during colonoscopy or lapratomy. Colonoscopy is the first choice for getting biopsy if ileocecal region in involved because ileocecal junction becomes incompetent and endoscope can cross it, therefore biopsy can be obtained.
5. **X-ray chest** – Active pulmonary disease is present in less than 50% of patients.

PRIMARY INTESTINAL TUBERCULOSIS

This type of tuberculosis results from ingestion of milk from cows infected by bovine strain of mycobacterium.

It is characterized by a small focus in the intestir and large mesenteric lymph nodes.

Presentation is similar to secondary intestinal tuberculosis such as abdominal pain, intestinal obstruction, weight loss and fever. There is palpable mass in ileocaecal region in more than 50% of cases, most often fixed and tender.

TUBERCULOSIS OF MESENTERIC LYMPH NODES

Tuberculosis of mesenteric lymph nodes may present as:

1. Chronic tuberculous mesenteric lymphadenitis with or without intestinal tuberculosis. Enlarged and palpable lymph nodes may cause suspicion of lymphoma.
2. Acute caseous tuberculous lymphadenitis causing tuberculous peritonitis
3. Peritoneal adhesions to tuberculous lymph nodes causing intestinal obstruction.

> - Tuberculosis of ovary & fallopian tubes
> - Tuberculosis of liver presents as fever, jaundice and hepatomegaly

MANAGEMENT

1. Rest
2. Anti-tuberculous chemotherapy for at least one year.
3. Indications for surgery: intestinal obstruction or perforation, or for establishing diagnosis.

INFLAMMATORY BOWEL DISEASE

Crohn's disease and ulcerative colitis are chronic inflammatory bowel diseases of relapsing and remitting course that usually extends over years.

A crucial distinction in both conditions is that ulcerative colitis only involves the colon, while Crohn's disease can involve any part of GI tract from anus to mouth.

Both diseases most commonly start in young adults, peak age 20-40 years. Second incidence peak is in persons aged over 60 years.

Both sexes are equally involved.

Exact cause is unknown, both genetic and environmental factors may be responsible.

> **FACTORS ASSOCIATED WITH INFLAMMATORY BOWEL DISEASE (IBS)**
>
> **Genetic**
> - More common in jewish people
> - 10% have a first – degree relative or at least one close relative with IBS.
> - More chances in identical twins
> - Associated with autoimmune thyroiditis and SLE.
> - HLA genes are important in ulcerative colitis but in Crohn's disease non- HLA genes may be important.
> - Patients with IBS with HLA –B27 commonly develop ankylosing spondylitis.
>
> **Environmental**
> - Associated with low – residue, high refined sugar diet.
> - Ulcerative colitis is less common in smokers.
> - Crohn's disease is more common in smokers.
> - Possible association with measles virus and atypical mycobacterial infection.

CROHN'S DISEASE

Crohn's disease is characterized by localized areas of non-specific, grannulomatous inflammation of the bowel. It can effect anywhere from mouth to anus, the most common sites involved, in order of frequency are:

- Terminal ileum and ascending colon (50%)
- Terminal ileum alone (30%)
- Colon alone(20%)
- Ileum and jejunum (rare)

INCIDENCE

- 5-10 per 100,000 per year
- Peak age 20-40 years, uncommon before age 10 years.
- Both sexes equally involved

PATHOLOGY

1. Entire wall of the bowel is edematous and thickened.

2. *Cobblestone appearance* of terminal ileum. There are deep ulcers, which appear as linear fissures so that the mucosa between them is described as *cobblestoned.*

3. The *deep ulcers* may penetrate through the bowel wall to initiate *abscess or fistulas*. The fistula may develop b/w adjacent loops of bowel or b/w bowel and bladder, uterus, or vagina.

4. Characteristically the changes are *patchy;* the inflammatory process is interrupted by islands of normal mucosa. Lesion in this pattern is called *skip lesion*.

5. Mesenteric lymph nodes are enlarged and mesentery thickened

6. Microscopically: Non- caseating granulomas are characteristic of Crohn's disease (The granulomas consist of focal aggregates of epitheloid histocytes surrounded by lymphocytes and contain giant cells).

CLINICAL FEATURES

Clinical features depend on region affected and extent of the disease.

ILEAL DISEASE

Obstructive features
Narrowing of the bowel may occur as a result of inflammation, spasm, or fibrotic stenosis resulting in postprandial bloating and cramping abdominal pains.

Abdominal pain:

- It is the commonest symptom
- It occurs mostly in right iliac fossa (because terminal ileum and right side of colon are most commonly involved)
- Colicky pain, which is usually situated in the mid or lower abdomen suggests intestinal obstruction, intra-abdominal abscess, an inflammatory mass. Pain may be associated with nausea, vomiting and borborygmi
- Exacerbations of pain may be accompanied by diarrhea and fever.

Diarrhea:
It is not as severe as in ulcerative colitis. Diarrhea is usually watery and does not contain blood or mucus.

Inflammatory features
Fever, malaise, weight loss and abdominal pain.

Steatorrhoea and malabsorption
Malabsorption results in weight loss, anemia and fat, protein and vitamin deficiency.

CROHN'S COLITIS

Crohn's disease involving colon presents just like ulcerative colitis such as **bloody diarrhea** and passage of mucus. Inflammatory features such as malaise, anorexia and weight loss are also present. No involvement of rectum and presence of perianal disease favors the diagnosis of Crohn's disease rather than ulcerative colitis.

CLINICAL EXAMINATION

1. Weight loss
2. Aphthous ulcerations of mouth
3. Local tenderness in right iliac fossa.
4. Palpable mass by abdominal or rectal examination : a mass may be palpable, formed of inflamed loops of bowel bound together or there may be an abscess.
5. Perianal disease: edematous anal tags, anal fissures or perianal abscesses are diagnostic and are common when colon is involved.

EXTRA-INTESTINAL MANIFESTATIONS OF INFLAMMATORY BOWEL DISEASE

Seronegative arthritis
- Acute arthritis affecting medium sized joints
- Sacroiliitis
- Ankylosing spondylitis

Dermatological
- Erythema nodosum
- Pyoderma gangrenosum
- Oral aphthous ulcers

Ocular
- Conjunctivitis, iritis, episcleritis

Hepatic and biliary
- Primary sclerosing cholangitis (ulcerative colitis only)
- Gallstone
- Autoimmune hepatitis
- Fatty liver
- Portal pyemia and liver abscess
- Amyloidosis
- Cholangiocarcinoma

Renal
- Oxalate calculi (small bowel Crohn's)
- Amyloidosis
- Ureteric obstruction (Crohn's)

Vascular
- DVT
- Portal or mesenteric vein thrombosis

COMPLICATIONS

1. **Abscess:** presence of tender abdominal mass with fever and leukocytosis suggests abscess. CT scan is required for diagnosis.
2. **Fistula:** The abscess may discharge into intestinal lumen or into bladder or vagina creating a fistula. Surgical treatment may be required.
3. **Intestinal obstruction:** it may result from active inflammation or chronic fibrotic stricture. Intravenous fluids, nasogastric suction and systemic steroids are given. Non-responders need surgical removal of stenotic area.
4. **Intestinal perforation:** unlike ulcerative colitis severe hemorrhage is uncommon in Crohn's disease.
5. **Increased risk of carcinoma** of colon in segments affected by Crohn's disease

DIFFERENTIAL DIAGNOSIS

Crohn's disease should be differentiated from other diseases as following:

Chronic cramping abdominal pain and diarrhea
- Irritable bowel syndrome

Acute fever and right iliac fossa pain
- Appendicitis
- Yersinia enteritis

Fever, abdominal pain, weight loss and similar X-rays
- Intestinal lymphoma

Right iliac fossa mass
- Appendicular abscess
- Tuberculosis
- Ulcerative colitis
- Actinomycosis
- Amebiasis

Features of colitis
- Ulcerative colitis
- Amebiasis
- Infectious colitis
- Diverticulitis
- Ischemic colitis

INVESTIGATIONS

Blood CP

- **Anemia:** as a result of chronic inflammation, mucosal blood loss, iron deficiency, or vitamin B12 deficiency due to terminal ileal inflammation.

- **Leukocytosis**: it reflects inflammation or abscess or secondary to corticosteroids.

ESR: raised due to inflammation.

Serum albumin:
Hypoalbuminemia results due to protein- losing enteropathy, malabsorption or chronic inflammation.

Stool analysis:
Stool analysis is performed to detect leukocytes, ova, parasites and clostridium. difficile toxin.

Barium follow-through
Finding related to Crohn's disease are ulcerations, strictures, and fistulas.

Barium enema:
It shows alteration of mucosal pattern, deep ulceration or string sign (marked narrowing of the affected segment)

Sigmoidoscopy and colonoscopy
They demonstrate exact extent of the disease, ulcers, strictures and segmental involvement.

Biopsy
Granulomas are identified in 25 % cases of Crohn's disease and are highly suggestive of this disease.

pANCA and ASCA
These investigations differentiate Crohn's disease from ulcerative colitis.

- Antineutrophil cytoplasmic antibodies with perinuclear staining (pANCA) are present in 60-70% of patients with ulcerative colitis and 5-10% cases of Crohn's disease.
- Antibodies to the yeast S cerevisae (ASCA) are found in 60-70% of patients with Crohn's disease and 10-25% patients with ulcerative colitis.

INVESTIGATIONS IN CROHN'S DISEASE

- Blood CP
- ESR
- Serum albumin
- Stool analysis
- Barium follow-through
- Barium enema
- Sigmoidoscopy and colonoscopy
- Biopsy
- pANCA and ASCA

TREATMENT

MEDICAL TREATMENT

Nutrition

Diet

- Avoid dairy products if flatulence or diarrhea is a main complaint as lactose intolerance is common in Crohn's disease.
- Fiber supplement- if colon is involved.
- Low- fiber diet in patients with features of intestinal obstruction.
- Low -fat diet
- Supplements of iron, folic acid, zinc, calcium, vitamins D & B12 & electrolytes may be required

Total Parenteral Nutrition (TPN)
TPN is used short- term in patients with active disease, high grade obstruction, severe diarrhea, or abdominal pain.

Symptomatic treatment of diarrhea

- Cholestyramine 2-4 g 2-3 times daily before meal to bind malabsorbed bile salts that are responsible for secretory diarrhea.
- Loperamide (cap. Imodium) 2-4 mg three times daily.

Specific drug therapy

Corticosteroids
Prednisolone (Tab. Deltacortil 5mg) 40-60mg/d, tapering after 2-3 weeks and continue for further 4-5 weeks. However chronic low dose steroid

(2.5-10mg/d) is often required. Chronic use of steroids should be avoided where possible because of their serious side –effects.

Side-effects

Aseptic necrosis of hip joint, cataract, osteoporosis, diabetes, hypertension and weight gain.

Immunosuppressive therapy

- ***Azathioprine***

  Azathioprine (Tab. Imuran 25mg) 1.5-2mg/kg/d as a long- term therapy. The mean time to symptomatic response is 4 months, therefore not useful for acute exacerbations.

  Indications for immunosuppressive therapy

  - Patient develops relapse after stopping the steroids
  - Patients requiring chronic steroid therapy. Azathioprine helps in elimination or reduction the dose of steroids in over 75% of cases.
  - Symptomatic fistulas

  Side effects

  Bone marrow suppression

- ***Infliximab***

  Infliximab is an anti- tumor necrosis factor antibody that demonstrated improvement in more than 80% of patients with moderate to severe Crohn's disease.

  Single dose of 5mg/kg IV gives response within 2 weeks that gradually diminishes over 3 months. Hypersensitive reaction may develop.

  At present Infliximab is the most useful treatment for patients with severe Crohn's disease to promote rapid initial improvement while azathioprine is being initiated (responding later).

5-aminosalicylic acid agents

Sulfasalazine (Tab. Salazopyrin 500mg) 2-4 tablets daily in 2-3 divided doses. Is effective when there is colonic involvement, not effective for small intestinal involvement.

MEDICAL MANAGEMENT OF CROHN'SDISEASE

- Selective balanced diet
- Cholestyramine or loperamide for diarrhea
- Steroids (prednisolone) for relapse
- Immunosuppressive therapy with azathioprine or mercaptopurine , infliximab--if chronic steroids therapy is required
- Remission may be maintained with the help of mesalamine (Asacol 800mg 3-times daily.

SURGICAL TREATMENT

About 50% of patients require surgery at some time during the course of their disease.

Indications for surgery

- Failure of medical therapy, with acute or chronic symptoms, producing ill-health
- Complications of crohn's disease e.g. toxic dilatation, obstruction, perforation, abscess, fistula.

Surgery consists of resection of small segment of bowel and end-to-end anastomosis

ULCERATIVE COLITIS

It is a chronic, relapsing and remitting, non-specific inflammatory disease of the colon, characterized by suppurative ulceration of the mucous membrane of the colon

INCIDENCE

- 5-10 per 100000/year
- Age 10-40 years
- More common in females
- Less common in smokers than in non-smokers

PATHOLOGY

The diseases may involve rectum, rectosigmoid, whole left side of colon or the whole colon.

- Rectosigmoid region (proctosigmoiditis)—50%
- Left sided colitis involving rectum, sigmoid and descending colon—30%
- It may involve the whole colon (total colitis)—20%
- It may involve distal terminal ileum when ileocecal valve is incompetent (backwash ileitis)

> **FACTORS ASSOCIATED WITH INFLAMMATORY BOWEL DISEASE (IBS)**
>
> **Genetic**
> - More common in jewish people
> - 10% have a first – degree relative or at least one close relative with IBS.
> - More chances in identical twins
> - Associated with autoimmune thyroiditis and SLE.
> - HLA –DR 103 associated with severe ulcerative colitis
> - Patients with IBS with HLA –B27 commonly develop ankylosing spondylitis.
>
> **Environmental**
> - Associated with low – residue, high refined sugar diet.
> - Ulcerative colitis is less common in smokers.
> - Crohn's disease is more common in smokers.
> - Appendicectomy protects against ulcerative colitis

- Macroscopically the mucosa looks reddened inflamed and bleed easily. With severe disease there is extensive ulceration, with adjacent mucosa appearing as inflammatory polyps.

  In fulminant disease most of the mucosa is lost, leaving a few island of edematous mucosa and toxic dilatation occurs.

- Microscopically the mucosa shows chronic inflammatory cell infiltrate. Crypt abscesses and goblet cell depletion are also seen.

CLINICAL FEATURES

1. Precipitating factors for relapse are emotional stress, intercurrent infection, gastroenteritis, antibiotics and NSAIDs.
2. The first attack is often the most severe and thereafter the disease is characterized by exacerbations and remissions.
3. Bloody diarrhea is hallmark of ulcerative colitis.
4. Disease may be mild, moderate or severe based on clinical features and laboratory parameters.

Mild disease

- Gradual onset of infrequent diarrhea (less than 4 stools per day) with intermittent rectal bleeding and mucus, urgency and tanesmus (feeling of incomplete bowel emptying).

- Left lower quadrant cramps relieved by defecation are common, but there is no significant abdominal tenderness.

Moderate disease

- There is more severe diarrhea with frequent bleeding.
- Abdominal pain and tenderness is present but not severe. There may be mild fever, anemia and hypoalbuminemia.

Severe disease

- Patient presents with more than 6-10 bloody diarrhea per day resulting in severe anemia, hypovolemia and impaired nutrition with hypoalbuminemia.

- Abdominal pain and tenderness are present.

Severe life –threatening (Fulminating type)
It is characterized by exhausting diarrhea and dehydration. There may be toxic dilatation of colon (toxic megacolon) with tachycardia, high fever, abdominal distension & tenderness. It is an emergency because patient may die from colonic perforation.

Chronic type
In chronic colitis the bowel is permanently damaged by fibrosis and behaves as rigid tube incapable of absorbing fluid properly or of acting as a fecal reservoir. Persistent diarrhea is the feature.

Disease severity assessment in ulcerative colitis		
	Mild	**Severe**
Daily bowel frequency	<4	>6
Blood in stool	+/-	+++
Stool volume (g/24hrs)	<200	>400
Pulse	<90	>90
Temperature (^{0}C)	Normal	> 37.5 2 days out of 4
Sigmoidoscopy	Normal or granular mucosa	Blood in lumen
Abdominal x-ray	Normal	Dilated bowel
Hemoglobin (g/dl	Normal	<10
ESR	<30	>30
Serum albumin (g/dl)	> 3.5	<3

Extra gastrointestinal manifestations are given in table in Crohn's disease.

INVESTIGATIONS

Blood CP/ESR
- Anemia
- Leukocytosis
- Raised ESR

Stool Culture to exclude infective cause

Sigmoidoscopy
- Features of ulcerative colitis on endoscopy are:
- Loss of mucosal vascularity
- Diffuse erythema
- Friability of the mucosa
- Presence of exudate consisting of mucus, blood and pus
- Ulcers are shallow
- Full colonoscopy should not be performed in the acutely ill patient because of risk of peroration.

Plain X-ray abdomen
Plain abdominal x-ray is obtained in severe colitis to look for significant colonic dilatation. When the transverse colon is dilated more than 6 cm, there is a high risk of colonic perforation and subsequent generalized peritonitis and death.

Barium enema
- It should not be performed during acute attack and where toxic dilatation is suspected because of risk of perforation
- Double contrast barium enema shows the severity and extent of the disease
- Radiological changes may be from granular appearance of colonic mucosa to severe ulceration. In chronic case there may be shortening of the colon with narrowing of the lumen

Colonoscopy
- It demonstrates the extent and severity of colitis, because barium enema may underestimate.
- Biopsy is also taken during colonoscopy

INVESTIGATIONS IN ULCERATIVE COLITIS

- CP/ESR
- Stool D/R, C/S
- Sigmoidoscopy
- Plain x-ray abdomen
- Barium enema
- colonoscopy

DIFFERENTIAL DIAGNOSIS

1. Infectious colitis
2. Amoebic colitis
3. Pseudomembranous colitis
4. Crohn's disease
5. Intestinal neoplasm
6. Diverticulitis
7. Ischemic colitis

COMPLICATIONS

Local complications

1. Ischiorectal abscess
2. Fistula in ano, rectovaginal fistula
3. Fibrous stricture of rectum or colon
4. Colonic perforation
5. Toxic dilatation of the colon – In severe acute attack it may occur & is manifested by abdominal distension. Pain X-ray abdomen shows a dilated thin-walled colon with a diameter greater than 6cm that is gas filled. If the patient does not settle in 48h with high dose of corticosteroid emergency surgery should be performed

   Carcinoma of colon. Incidence is 1% per year after 10 years of diagnosis of ulcerative colitis i-e 20% risk after 30 years.

SYSTEMIC COMPLICATIONS

Seronegative arthritis

- Acute arthritis affecting medium sized joints
- Sacroiliitis
- Ankylosing spondylitis

Dermatological

- Erythema nodosum
- Pyoderma gangrenosum
- Oral aphthous ulcers

Ocular

- Conjunctivitis, iritis, episcleritis

Hepatic and biliary

- Primary sclerosing cholangitis (ulcerative colitis only)
- Gallstone
- Autoimmune hepatitis
- Fatty liver
- Portal pyemia and liver abscess
- Amyloidosis
- Cholangiocarcinoma

Renal

- Oxalate calculi (small bowel Crohn's)
- Amyloidosis
- Ureteric obstruction (Crohn's)

Vascular

- DVT
- Portal or mesenteric vein thrombosis

TREATMENT

There are two main treatment objectives:

- To terminate the acute, symptomatic attack.
- To prevent recurrence of attack.

General measures

- Caffeine and gas producing vegetables should be avoided.
- Fiber supplement decreases diarrhea and rectal symptoms.
- Anti-diarrheal drugs should not be given during acute attack however they are safe in patients with mild chronic symptoms.

Specific medical treatment

Distal colitis
(confined to rectum or rectosigmoid)

- *Mesalazine (Asacol) enema:* 4g at bedtime for 3-12 weeks with 75% of patients improving.
  OR
- *Hydrocortisone enema*: (80-100 mg). It is less effective than mesalazine.

- Patients not responding to topical treatment should be considered for systemic steroids.

Mild to moderate colitis
(Disease extending above the sigmoid colon)

- *Sulfasalazine (Salazopyrin 500mg)* twice daily, increased gradually over 1-2 weeks to 2g twice daily. Most patients improve within 3 weeks, though some require 2-3 months. Folic acid 1mg/d should be given to all patients taking sulfasalazine. Mesalazine (Asacol 400mg) 800mg three times daily is given in patients intolerant to sulfasalazine.

  Side effects: nausea, vomiting, headache, reversible azoospermia, hemolytic anemia and agranulocytosis.

- *Steroids:* patient not improving after 2-3 weeks of mesalazine therapy should have the addition of corticosteroid therapy. Hydrocortisone enema is first tried, if no improvement after 2 weeks then systemic steroids are started. Prednisolone 20-30 mg twice daily for 2 weeks then taper the dose not more than 5mg/week.

Severe colitis

General measures
- Discontinue all oral intake with total parenteral nutrition.
- Avoid all opiates or anticholinergics.
- Restore circulatory volume with fluids and blood as needed.
- Frequent abdominal examination for tenderness and peritonitis.
- Obtain plain x-ray abdomen to look for colonic dilation.
- Obtain a surgical consult.
- Send stool for C/S, ova and parasites.

Corticosteroid therapy
- Methylprednisolone (Inj. Solu- Medrol) 40-80mg daily by continuous infusion.
- Hydrocortisone enema 100mg over 30min 2-times daily.
- 50-70% patients get remission within 7-10 days. After improvement oral fluids are started and then steroids should be given orally as prednisolone.

Immunosuppressive therapy
- Intravenous cyclosporine benefits over 75% of patients with severe colitis not responding to 7-10 days therapy of steroids.

- Patients who relapse frequently after steroid therapy or require maintenance steroid therapy may be given azathioprine (1.5-2mg/kg/d); maximal effect after 6-12 weeks, therefore steroid should be continued till that time.

  Side effects bone marrow suppression, nausea, vomiting and pancreatitis.

Surgical treatment

Indications
- Patient with severe disease not responding to corticosteroids for 7-10 days.
- Patient with toxic dilatation of colon not responding within 48-72 hours, to prevent perforation.
- Perforation
- Severe hemorrhage
- Chronic illness – Stricture formation

Procedure
Proctocolectomy (removal of rectum and colon) with ileostomy (connecting ileum to the body surface).

TOXIC MEGACOLON
Toxic megacolon develops in less than 2% of ulcerative colitis and is characterized by colonic dilation of more than 6cm on plain x-ray abdomen. All measure stated in severe colitis are performed

along with nasogastric suction and antibiotics to cover gram negatives and anaerobes.

THERAPY TO PREVENT RELAPSE

Chronic maintenance therapy is performed with:

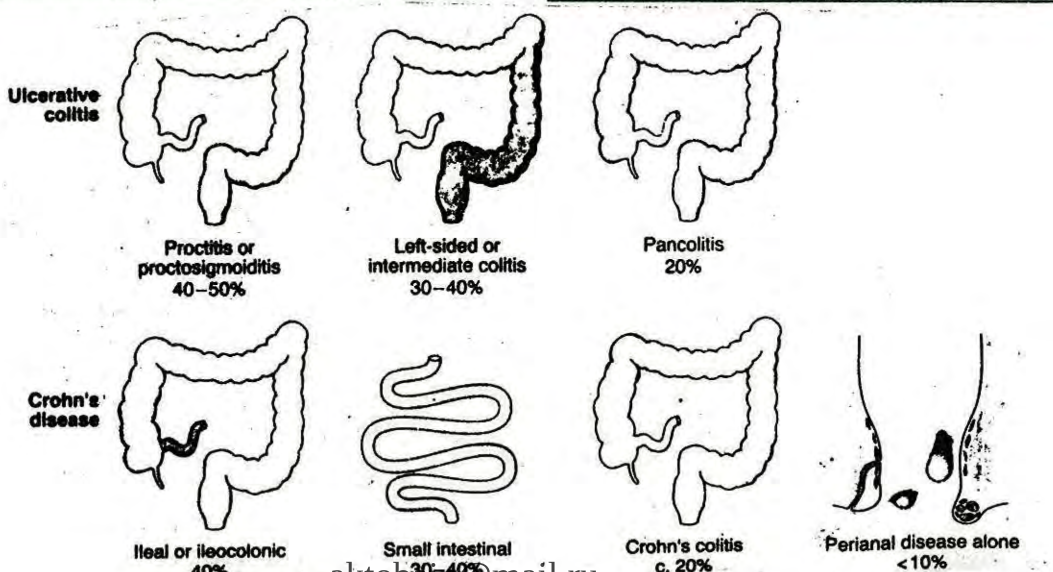
- Sulfasalazine 1-1.5 g twice daily OR mesalazine 800mg three times daily reduces the relapse in less than 33%.
- Therapy with azathioprine may be tried in patients not responding to sufasalazine or mesalazine or corticosteroids or who require chronic steroids. Consider surgical resection also.

CONDITIONS WHICH CAN MIMIC ULCERATIVE OR CROHN'S COLITIS

Infective	Non- infective
Bacterial • Salmonella • Shigella • Campylobacter jejuni • Enteropathic E.coli • Gonococcal proctitis • Pseudomembranous colitis	**Vascular** Ischemic colitis Radiation proctitis **Drugs** NSAIDs **Neoplastic** Colon carcinoma
Viral • Herpes simplex colitis • Chlamydia proctitis	**Idiopathic** Bachet's disease
Protozoal • Amebiasis	**Other** Diverticulitis

Comparison of extra-intestinal manifestations in Crohn's disease and ulcerative colitis

Organ	Crohn's	Ulcerative colitis
Eyes Uveitis, episcleritis conjunctivitis	3-10%	5-8%
Kidney Stones	30%	-
Gallbladder Stones	30%	5%
Liver Sclerosing cholingitis	<1%	3-10%
Fatty change	common	common
Chronic hepatitis	uncommon	uncommon
Cirrhosis	uncommon	uncommon
Skin Erythema nodosum	5-10%	2%
Pyoderma gangrenosum	1%	1-2%
Joints Ankylosing spondylitis	2-6%	1-2%
Monoarticular arthritis	14%	10-15%
Sacroiliitis	<15%	12-15%



DIARRHEA

Increase in the stool weight to greater then 250g per day accompanied by increased frequency and liquidity of stool is called diarrhea

Acute diarrhea

Diarrhea lasting less than 2 weeks is called acute diarrhea. It may result from emotional stress, food intolerance, organic substances (e.g. mushrooms, shellfish), drugs and infectious agents (including viruses, bacteria and protozoa).

Chronic diarrhea

Diarrhea that persists for more than 2 weeks is called chronic diarrhea. It may be divided into six categories such as osmotic, secretory, inflammatory, malabsorptive, chronic infectious, and motility disorder diarrhea.

ACUTE INFECTIOUS DIARRHEA (GASTROENTERITIS)

Acute infectious diarrhea is divided into two groups as following:

Inflammatory or bloody diarrhea

Inflammatory diarrhea suggests involvement of large intestine by invasive bacteria or parasites or toxins. Clinically patient presents with frequent bloody, small-volume stools, often associated with fever, abdominal cramps, tanesmus and fecal urgency.

Non-inflammatory diarrhea

Non-inflammatory diarrhea is generally a milder disease and is caused by viruses, or toxins that affect the small intestine and interfere salt and water balance, resulting in large- volume watery diarrhea, often with nausea, vomiting and cramps.

Food poisoning

The disease caused by toxins present in consumed foods is called food poisoning.

- When the incubation period is short (1-6 hours after consumption), the toxin is preformed and present in the contaminated food. Vomiting is usually a major complaint, and fever is usually absent. Examples are toxins produced by S. aureus or Bacillus cereus, and toxin can be detected in the food.

- When the incubation period is longer (8-16 hours) the organism is present in the food and produces toxin after being ingested. Vomiting is less prominent, abdominal cramps are frequent and fever is often absent. Example is disease caused by clostridium perfringens.

PATHOGENESIS

Following are mechanisms through which infectious diarrhea is produced:

Non-inflammatory diarrhea

Enterotoxin- mediated diarrhea

In this group organism does not invade the intestinal mucosa and its effects are mediated by its enterotoxin (exotoxin). There is no inflammation of intestinal mucosa. Following organism produce exotoxin- mediated diarrhea.

- Vibrio cholerae
- E. coli –toxigenic
- Staphylococcus aureus
- Clostridium perfringens

Non- invasive organisms

The organism exists in the intestinal lumen and does not invade the tissue. Organism is Giardia.

Inflammatory (invasive) diarrhea

In this group of infections, the infectious agent invades the intestinal mucosa causing acute inflammation of the intestine. Following organisms produce invasive intestinal infections.

- Viruses: Adenovirus, cytomegalovirus
- Bacteria: salmonella, shigella, campylobacter.
- Parasites: Entameba histolytica.

CAUSES OF INFECTIOUS DIARRHEA	
Non-inflammatory diarrhea	**Inflammatory diarrhea**
Viral • Rotavirus • Norwalk virus	**Viral** • Cytomegalovirus
Protozoa • Giardia • Cryptosporidium	**Protozoa** • Entameba histolytica
Bacterial *Preformed enterotoxin* • S. aureus • Bacillus cereus • Clostridium perfringens *Enterotoxin production* • Enterotoxigenic E.coli • Vibrio cholerae	**Bacterial** *Cytotoxin production* • Clostridium difficile *Mucosal invasion* • Shigella • Salmonella • Compylobacter • Yersinia • Chlamydia • N. gonorrhea • Listeria monocytogenes

CLINICAL FEATURES

Severity of diarrhea can divided as:

Mild: three or fewer stools per day.

Moderate: four or more stools per day in association with local symptoms such as abdominal cramps, nausea, tanesmus.

Severe: four or more stools per day with systemic symptoms such as fever, chills and dehydration.

COMPLICATIONS OF GASTROENTERITIS

- Circulatory shock
- Acute renal failure
- Electrolyte depletion leading to lethargy and paralytic ileus.
- Metabolic acidosis

Features suggesting infectious diarrhea

- Similar recent illness in a family member suggests an infectious cause.
- Recent ingestion of improperly stored or prepared food implicates food poisoning, especially if other people were similarly affected.
- Exposure to unpurified water as in camping.
- Recent travel aboard causing traveler's diarrhea.
- Antibiotic administration within the preceding several weeks increases the likelihood of clostridium difficile colitis.

Symptoms

Patient with acute infectious diarrhea presents with nausea, vomiting, abdominal pain; fever, and diarrhea, which may be watery, or bloody, depending on the specific pathogen.

Signs

Examination of patient includes assessment of:

- General appearance
- Mental status
- Dehydration manifesting as dry mouth, inelastic skin, decreased urination, weakness, lethargy and sunken eyes depending on degree of dehydration.
- Examination of abdomen for tenderness or peritonitis.
- Features of metabolic acidosis especially in children.

INVESTIGATIONS

1. ***Stool analysis***

   Stool examination is performed to detect:

   Fecal leukocytes:

   - *Always present:* in shigella, campylobacter and entroinvasive E.coli, also inulcerative colitis and Crohn's disease.
   - *Variable:* in salmonella, clostridium difficile
   - *Absent:* in rotavirus, giardia, entameba, cryptosporium, E.coli, food poisoning due to S. aureus, bacillus cereus, and clostridium perfringens.

   Ova, parasites and clostridium difficile toxin

2. Stool culture in bloody diarrhea
3. Serum electrolytes
4. Serum urea and creatinine
5. Sigmoidoscopy if ulcerative colitis is suspected

MANAGEMENT

Diet

- Soft easily digested diet such as soups is preferred.
- Frequent feedings of fruit drinks, tea, cold-drinks are encouraged.
- Rest bowel by avoiding high fiber diet, fats, milk products, caffeine and alcohol.

Rehydration

- *Oral rehydration solution (ORS)*
  It is inexpensive, safe and highly effective in almost all awake patients. Fluids should be given at the rate of 50-200 ml/kg/d depending on the hydration state.

- *Intravenous fluids*
  Intravenous fluids are preferred in patients with severe dehydration. Normal saline or Ringolactate is given to restore water and electrolytes. Dextrose water should be avoided.

Anti-diarrheal agents

Anti- diarrheal agents may be used in patients with mild to moderate diarrhea to improve patient comfort. However they should not be used in patients with bloody diarrhea, high fever, or systemic toxicity for fear of worsening the disease. Loperamide (Cap. Imodium 2mg) is preferred in a dosage of 4mg initially, followed by 2mg after each loose stool (maximum 16mg/24 h.

Antibiotic therapy

Empirical treatment

- Because majority of patients has mild, self-limiting disease due to viruses or nonivasive bacteria, empirical antibiotic treatment of all patients with acute diarrhea is not recommended.
- Empirical treatment should be given to patients in whom an invasive bacterial infection is suggested by the presence of moderate to severe fever, tanesmus, bloody stool, presence of fecal leukocytes while the stool bacterial culture is in process.
- The drug of choice is quinolone such as ciprofloxacin (Ciproxin) 500mg twice daily for 5-7 days. Empirical therapy with metronidazole (Flagyl) 250-500mg four times daily may be given if Giardia is suspected because it may be negative in stools of 50% of

Organism	Incubation period (hours)	Vomiting	Diarrhea	Fever	Pathogenesis
Staphylococcus	1-8	+++	+	-	Enterotoxin
Bacillus cereus	1-8	+++	+	-	Enterotoxin
Clostridium perfringens	8-16	+	+++	-	Enterotoxin
E.coli	24-72	+	+	-	Enterotoxin
Vibrio cholerae	24-72	+	+++	-	Enterotoxin
Campylobacter	2-10 days	-	+++	+	Invasion and enterotoxin
Shigella	24-72	+	+	+	Invasion
Salmonella	8-48	+	+	+	Invasion
Yersinia	?	+	+	+	invasion

GASTROENTERITIS
EMERGENCY ROOM NOTE

History

- Ask about the predisposing factors such as ingestion of improperly stored food, food from outside, involvement of any other person in home.
- Ask about volume and number of loose motions, presence of blood, mucus in the stool, history of tanesmus, fever.
- Ask about complications such as low urine output.

Examination

- Examine vitals; BP, pulse, temperature and respiratory rate.
- Mental status of patient such as alert, drowsy confused or comatose.
- Signs of dehydration such as sunken eyes, cold clammy inelastic skin, and dry tongue.
- Metabolic acidosis: tachypnea
- Urine output

Investigations

Blood CP

Look for leukocytosis and level of hemoglobin (reading may be falsely high due to hemoconcentration due to dehydration).

Urea, creatinine and electrolytes

Pre- renal type of renal failure may develop, electrolyte imbalance such as hyponatremia, hypokalemia and low bicarbonate may be present.

Stool D/R

Look for presence of leukocytes, blood, ova and parasites.

Stool C/S

Stool culture is performed in case of bloody diarrhea and fever

Management

- Fluid replacement with normal saline or Ringolactate as much as required, monitor urine output, look JVP, auscultate basal crepts to avoid overhydration, do not give dextrose water.
- Inj. Marzine or Gravinate I/M for vomiting
- Antibiotics if necessary. Inj. Ciprofloxacin 500mg I/V 12 hourly.

CHRONIC DIARRHEA

Diarrhea continuing for weeks or months, either persistent or intermittent is called chronic diarrhea.

CLASSIFICATION OF CHRONIC DIARRHEA

Osmotic Diarrhea

Osmotic diarrhea is caused by ingestion or malabsorption of an osmotically active substance that exerts an osmotic force that draws fluid into the intestinal lumen. The increased intestinal fluid volume exceeds the capacity of colon for reabsorption resulting in diarrhea.

Clinical features

- Bulky, greasy, foul smelling stools, weight loss, nutrition deficiencies.
- Diarrhea improves with fasting.
- Increased stool osmotic gap.

Causes

The most common causes of osmotic diarrhea are:

- *Lactase deficiency*: it may be congenital or acquired after an episode of viral gastroenteritis, medical illness or GI surgery.
- *Laxative abuse*
- *Malabsorptive syndromes* such as pancreatic insufficiency, Celiac disease, Whipple's disease and bacterial over growth.

Secretory diarrhea

In this disorder there is active intestinal secretion of fluid and electrolytes as well as decreased absorption resulting in diarrhea that may be large in volume (1-10 L/d) but with a normal osmotic gap. Food does not affect the diarrhea and it continues during fasting.

Causes

- Zollinger-Ellison syndrome
- Carcinoid syndrome
- VIPoma
- Medullary carcinoma of thyroid
- Bile salt malabsorption due to Crohn's disease or ileal resection.
- Villous adenoma of rectum.

Inflammatory diarrhea

Inflammatory diarrhea develops due to damage to the intestinal mucosal cells so that there is impaired intestinal absorption and excessive secretion of fluid resulting in diarrhea that may contain blood. Patient presents with fever, abdominal tenderness, and blood or leukocytes in stool.

Causes

- Ulcerative colitis
- Crohn's disease
- Eosinophilic gastroenteritis
- Malignancy e.g. lymphoma, colonic carcinoma with obstruction and pseudodiarrhea.

Abnormal motility diarrhea

It is not true diarrhea because in this condition volume and weight of stool is not increased but frequency of defection occurs due to rapid transit or to stasis of intestinal contents with bacterial overgrowth, resulting in malabsorption and diarrhea.

Causes

- Irritable bowel syndrome
- Diabetic neuropathy
- Thyrotoxicosis

Diarrhea due to chronic infections

Causes are Giardia lamblia, Entameba histolytica, and abdominal tuberculosis.

COMMON CAUSES OF CHRONIC DIARRHOEA

Infections

- Amoebiasis, Giardiasis
- Tuberculous enteritis

Inflammatory bowel disease

- Ulcerative colitis
- Crohn's disease

Endocrine disorders

- Thyrotoxicosis
- Diabetic autonomic neuropathy

Miscellaneous

- Malabsorption
- Irritable bowel syndrome
- Laxative abuse

EVALUATION OF PATIENT

There is a long list of investigations for the diagnosis of etiology of chronic diarrhea, therefore patient should be evaluated whether he has small bowel (right-sided) diarrhea or large bowel (left- sided) diarrhea:

Right sided, or small bowel diarrhea	Left sided, or large bowel diarrhea
Large stool volume	Small amount of stool
Increased frequency with large volume stool	Increased frequency with small volume stool
No urgency	Urgency
No tenesmus	Tenesmus present
No mucus	Mucus in stool
No blood	Blood may be present in stool
Central abdominal pain	Pain in left iliac fossa relieved by defecation

INVESTIGATIONS

Stool analysis

24- hour stool collection for weight and quantitative fat.

- Stool weight more than 300-g/24 h confirms the presence of diarrhea.
- Fecal fat more than 10g/24h indicates malabsorptive process.

Stool osmolality

An osmotic gap confirms osmotic diarrhea.

Fecal leukocytes

The presence of fecal leukocytes implies an underlying inflammatory process.

Stool for ova and parasites

Entameba and Giardia may be present.

Proctosigmoidoscopy
It may be required if inflammatory bowel disease is suspected.

Upper GI endoscopy with small bowel biopsy
It is performed if malabsorption is suspected.

Barium meal or follow through
Barium studies may be helpful for diagnosis of Crohn's disease, lymphoma or carcinoid tumors.

Blood tests
Deficiency of particular nutrient helps in identification of site of its absorption and other factors that are required for digestion and absorption.

- Blood CP-- anemia occurs due to iron, B12 or folic acid deficiency.
- Electrolytes—hyponatremia in secretory diarrhea
- Calcium, phosphorus, albumin, PT—deranged due to malabsorption of fat- soluble vitamins.

MANAGEMENT OF CHRONIC DIARRHEA

- Treatment of the cause.
- Anti-diarrheal drugs such as loperamide (Imodium 2mg) 4mg initially then 2mg after each loose stool (max 16mg/d).
- Octreotide (Inj. Sandostatin) for secretory diarrhea due to VIPoma and carcinoid tumors.
- Cholestyramine for bile- salt induced diarrhea due to ileal disease.

POLYPS OF LARGE INTESTINE

Neoplastic polyps
They are classified histologically into tubular adenoma, tubular villous adenoma and villous adenoma. The later two increase the risk of malignancy

- They are mostly asymptomatic
- They may cause bleeding or discharge of mucus
- They may be detected by double contrast barium enema or by colonoscopy
- Polyp in the rectum can be removed at sigmoidoscopy and polyp in the colon at colonoscopy. If polyp is malignant, then resect that portion of colon from which the polyp was originated.

Familial adenomatous polyposis

- It is transmitted by autosomal dominant inheritance
- It is characterized by thousands of small polyps diffusely scattered on the mucosa of colon & rectum.
- They become malignant in 15 years
- Diagnosis on colonoscopy of members of affected family
- Treatment is removal of colon & rectum with permanent ileostomy

COLORECTAL CARCINOMA

- Carcinoma of large intestine is the commonest malignant tumor of GIT.
- Incidence: 40 per 100,000
- Age: 60-65 years
- Low incidence in patients taking aspirin and other NSAIDs.

PREDISPOSING FACTORS

Age
Incidence increases after age 40, and 90% of cases occur in patients over 50 years.

Low fiber diet
Low fiber diet causes intestinal stasis, increasing the time for which any potential carcinogen is in contact with the bowel wall.

Ulcerative colitis
It increases the risk after 7-10 years. 5-10% after 20 years and 20% after 30 years.

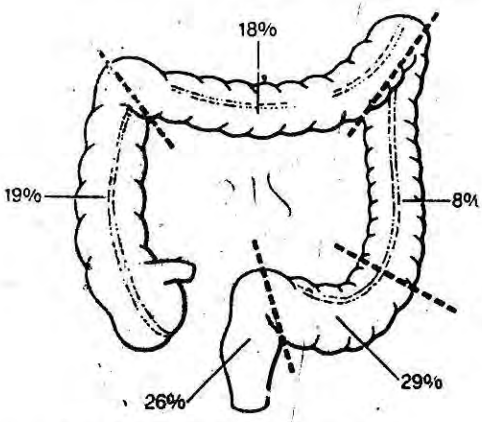
Familial polyposis syndrome
This is autosomal dominant condition that also predisposes the malignancy.

Hereditary nonpolyposis colorectal cancer is an autosomal dominant condition that markedly increases the risk of developing colorectal cancer.

Family history: a family history of colorectal carcinoma is present in 25% of patients with colon cancer. Risk increases 2-3 fold in case of family member has colon cancer.

PATHOLOGY

- Two-thirds of carcinomas occur in rectosigmoid area
- Tumor is usually polypoid mass with ulceration
- Spread: tumor spreads by direct infiltration through the bowel wall. It then invades the lymphatics and blood vessels
- Metastasis: early metastasis involves liver



Distribution of cancer of the large intestine.

CLINICAL FEATURES

Cancer of the left side of the colon

Symptoms]

1. *Change in bowel habit:*
   Alternative constipation and diarrhea is typical of annular carcinoma of the left colon. Initial stage is constipation due to intestinal obstruction, followed by sudden episode of colic with diarrhea. The diarrhea is due to liquefaction of feces above the obstruction caused by excess secretion of mucus by the colonic mucosa.
2. *Pain:*
   There may be mild lower abdominal pain, sometimes with severe colicky exacerbations.
3. *Bleeding:*
   Uncommon if present, mixed with faces
4. *Anorexia & Weight loss*

Signs

1. Palpable mass in the left iliac fossa
2. Liver metastasis may be found with hepatomegaly
3. Rectal examination: may demonstrate the tumor

Cancer of right side of the colon (cecum)

Symptoms

1. *Mostly asymptomatic*
2. *Pain:* dull ache in right iliac fossa is common
3. *Anemia* due to chronic persistent mild bleeding of the tumor
4. *Anorexia and loss of weight*
5. *Change in bowel habits:* No such prominent symptom as in left-sided tumor. There may be constipation or diarrhea but not alternating

Signs:

1. Palpable lump in the right iliac fossa
2. Tenderness & some guarding in right iliac fossa
3. Rectal examination is normal but the feces may contain blood

STAGING

Dukes staging of colorectal cancer

Stage	tumor spread	5-year survival rate (%)
A	Mucosa only	>95
B1	Submucosa or muscularis propia	90
B2	Submucosa	75
C1	muscularis + lymph node involvement	75
C2	subserosa + nodal involvement	25-50

INVESTIGATIONS

1. **Colonoscopy & sigmoidoscopy:** They are investigations of choice. Colonoscopy permits biopsy for histopathologic confirmation of malignancy.
2. **Barium enema:** It demonstrates advanced cancer or filling defect or stricture
3. **CT Scan abdomen:** To detect hepatic metastasis.
4. **Carcinoembryonic antigen (CEA):** It is elevated in 70% of patients with proved colorectal cancer but its level poorly correlate with cancer stage. It declines after surgery; if it rises again it indicates recurrence.
5. **LFTs:** abnormal LFTS indicate liver metastasis.

MANAGEMENT

- The resection of the tumor is the treatment of choice. Carcinoma of rectum may require removal of the rectum with permanent colostomy.
- Adjuvant chemotherapy increases survival in patients with stage C colon cancer. When combined with radiotherapy, chemotherapy increases survival in stage C of rectal cancer. Chemotherapy is of little benefit for patients with stage A or B. 5-fluorouracil and raltitrexed are most commonly used.

FUNCTIONAL BOWEL DISEASE

A functional disorder is one for which no structural, infective or biochemical cause can be found

ETIOLOGY

Anxiety, depression, stress.

Common Symptoms

- Dry mouth
- Sensation of lump in the throat
- Anorexia, nausea, vomiting
- Abdominal pain or discomfort
- Constipation or diarrhea

Chronic GI symptoms suggestive of psychomotor disorders

- Nausea alone
- Vomiting alone
- Bad breath (halitosis)
- Belching
- Abdominal bloating
- Chronic right hypochondrial pain
- Left iliac fossa pain
- Frequent bowel actions in morning

IRRITABLE BOWEL SYNDROME

(Spastic colon)

Etiology and pathogenesis

Anxiety, tension and excessive worries produce disturbance of motility in the colon resulting in disturbed bowel habit by diarrhea or constipation occurring alone or alternating. Disturbed motility is also found in esophagus, stomach, small intestine and bladder.

Certain foods may precipitate symptoms.

Incidence

- Age: 20-40 years
- Sex: common in women

Clinical features

Pain

- Pain in left or right iliac fossa or hypogastrium
- Pain occurs in attacks, usually relieved by defecation and sometimes provoked by food

Diarrhea:

- Painless, characteristically occurs in the morning, and almost never at night
- Ribbon like stools or without mucus is a common complaint
- An urge to defecate after meals occur due to exaggerated gastrocolic reflex
- A sensation of incomplete emptying of the rectum

Heartburn

Frequency and dysuria

Investigations

Organic bowel disease should be excluded by:

- Sigmoidoscopy
- Barium enema

Management

Reassurance

Reassure the patient about benign nature of the disease.

Constipation

- High fiber diet (Fiberad or Ispaghula husk)
- Bulk laxatives e.g. methyl cellulose
- Patient avoid chemical laxatives

Diarrhea & pain

- Antispasmodics such as mebeverine (Tab. Colofac 135 mg) three times daily 20min before meal.
- Antidepressants may be required.
- Dietary restriction: Avoidance of fresh fruits and salad
- Codeine phosphate (30 mg TDS)

DYSPEPSIA

(Non-ulcer dyspepsia)

Dyspepsia is a term used as a collective description for a variety of alimentary symptoms

> **SYMPTOMS INCLUDED IN THE TERM DYSPEPSIS**
>
> - Upper abdominal pain which may or not be related to food
> - Gastro-oesophageal regurgitation and heartburn
> - Anorexia nausea and vomiting
> - Early repletion or satiety after meals
> - A sense of abdominal distension or 'bloating'
> - Flatulence (burping, belching) and aerophagy

Pathogenesis

Dyspepsia is most commonly associated with organic diseases of the upper GIT such as peptic esophagitis, peptic ulcer, or gastric carcinoma. When all such causes are excluded, there remains a large group of people who complain of persistent dyspepsia for which no cause can be found. Such patients are considered to have non-ulcer or functional dyspepsia. It is believe that symptoms are generated by disturbance in the motor function of the alimentary tract due to some psychological factors.

Patients are usually young (below 40 years) and women are affected twice as commonly as men.

Clinical features

1. Upper abdominal pain which may or not be related to food.
2. Nausea and bloating (sense of abdominal distension) after meals
3. Pain & nausea characteristically occur on waking in the morning
4. Early satiety, flatulence and belching
5. Associated features of irritable bowel syndrome.

Diagnosis

1. Patient appears anxious in most of the cases. He may admit worries concerned about finance or family affairs. He may give history of previous psychotropic medication
2. In young women pregnancy should be ruled out
3. In old age exclude the intra-abdominal malignancy
4. Liver should be palpated & if necessary LFTs should be done

Investigations

- No diagnostic investigation
- In old age endoscopy or barium meal should be carried out to resolve doubt of malignancy

Management

1. Reassurance
2. Stop smoking and alcohol
3. Antacids
4. Appetite stimulant drugs e.g. metoclopramide (maxolon) 10 mg TDS
5. H2 – receptor antagonists e.g. famotidine (Nocid 20mg) may be tried if night pain or heartburn are troublesome.

PSYCHOGENIC VOMITING

- Usually it commences on wakening or immediately after breakfast
- There may be retching alone or the vomiting of gastric secretion or food.
- Vomiting occurs for a long time but no weight loss

- It should be differntiated from other causes of early morning vomiting e.g. pregnancy and alcohol abuse.

Management
- Remove psychological disturbance
- Tranquilizers e.g. – Tab. Xanax 0.5 mg B.D.
- Antiemetic e.g. metoclopramide (Maxolon) 10 mg TDS.

GLOBUS HYSTERICUS
- It describes the sensation of a lump in the throat which is not related to swallowing and even may be relieved swallowing food or drink.
- Barium swallow & endoscopy should be performed to exclude any organic disease.

VOMITING

Vomiting is the forceful ejection of gastric contents through mouth.

PHASES

There are three phases:
- **Nausea:** it is a feeling of wanting to vomit often associated with autonomic effects including hypersalivation, pallor and sweating.
- **Retching:** it is a strong involuntary effort to vomit.
- **Vomiting:** it is thee expulsion of gastric contents through the mouth.

MECHANISM
Vomiting is controlled by vomiting centers that are located in medulla and are stimulated by four different sources of afferent inputs such as:
1. Gastric or biliary distension, mucosal or peritoneal irritation, or infection.
2. The vastibular system which may be stimulated by motion or infection (vastibular neuronitis).
3. Higher CNS centers disorders, sights, smells, or emotional experiences, which may induce vomiting.
4. Stimulation of chemoreceptor trigger zone by drugs, toxins, hypoxia, uremia and radiation therapy.

CAUSES OF VOMITING	
Infections Gastroenteritis Hepatitis UTI **Drugs** NSAIDs Antibiotics Opiates Digoxin Cytotoxic drugs **GI diseases** Chronic peptic ulcer Gastric outlet obstruction Gastric cancer Gastroparesis	**Acute abdominal disorders** Appendicitis Cholecystitis Pancreatitis Intestinal obstruction **CNS disorders** Vestibular neuronitis Migraine Meningitis Raised intracranial pressure **Metabolic** Diabetic ketoacidosis Renal failure Addison's disease **Others** Severe pain Psychogenic Alcoholism

EVALUATION OF PATIENT
- Persistent vomiting suggests pregnancy, gastric outlet obstruction, gastroparesis, and psychogenic disorders.
- Vomiting immediately after meals strongly suggests bulimia.
- If intestinal obstruction is suspected, perform X-ray abdomen erect posture that shows dilated loops of small bowel.
- Perform serum electrolytes as the hypokalemia and metabolic alkalosis may be present.

COMPLICATIONS
- Dehydration
- Hypokalemia
- Metabolic alkalosis
- Aspiration, rupture of the esophagus
- Mallory-Weiss syndrome.

MANAGEMENT

Antihistamines

- Cyclizine (Marzine)
- Dimenhydrinate (Gravinate)

Dopamine antagonists

- Domperidone (Motilium)
- Metoclopramide (Maxolon)
- Promethazine (Phenergin)

Corticosteroids

- Dexamethasone for chemotherapy induced vomiting.

CONSTIPATION

This may be defined as infrequent passage of hard stools.

Management

1. High fiber diet, fiber supplements such as ispaghula husk, bran powder. Fiberad is pharmaceutical product of Abbot.
2. Laxatives & enemas.

Complications of constipation

- Hemorrhoids
- Anal fissure
- Rectal prolapse
- Fecal impaction
- Colonic volvulus
- Colonic perforations
- Fecal incontinence
- Urinary retention

CAUSES OF CONSTIPATION

GASTROINTESTINAL DISORDERS	NON- GASTROINTESTINAL DISORDERS
Dietary Lack of fiber and liquid **Structural** Colonic carcinoma Benign strictures **Motility** • Irritable bowel syndrome • Drugs • Chronic intestinal pseudo-obstruction • Hirschsprung's disease **Defecation** • Anorectal disease • hemorrhoids	**Drugs** • Opiates • Anticholinergics • Calcium antagonists • Iron supplement • Aluminium containing antacids **Metabolic/endocrine** • Diabetes • Hypercalcemia • Hypothyroidism • Pregnancy **Neurological** • Multiple sclerosis • Spinal cord lesion • Stroke • Parkinsonism **Others** Any serious illness with immobility, especially in the elderly.

LAXATIVES AND ENEMAS	MECHANISM OF ACTION
Bulking agents • Dietary fiber • Wheat bran • Ispaghula husk	Increased fecal mass due to fibers and water
Stimulant laxatives • Bisacodyl (Dulcolax) • Glycerol • Anthraquinones Senna (Senokot) Sodium picosulphate(Laxoberon	Stimulate intestinal secretion
Osmotic laxatives • Magnesium sulfate • Lactulose (Lactodil)	Osmotic effect
Enemas • Sodium phosphate (Kleen enema)	

ABDOMINAL PAIN

ACUTE ABDOMEN

This is a term used to define a group of abdominal conditions in which early surgical treatment must be considered. Few medical conditions mimic surgical conditions and some times un-necessary surgery is performed e.g some patients with myocardial infarction just present with epigatric pain and vomiting, patient of diabetic ketoacidosis or porphyria may present with abdominal pain. Therefore proper history and examination is required. This is very important topic for MCQs and viva.

Surgical causes of acute abdomen	
Inflammation • Appendicitis • Cholecystitis • Pancreatitis • Pyelonephritis • Intra-abdominal abscess • Salpingitis • Pelvic inflammatory disease **Perforation/rupture** • Peptic ulcer • Ovarian cyst • Diverticular disease	**Vascular/ ischemia** • Ruptured aortic aneurysm • Mesenteric infarction **Obstruction** • Intestinal obstruction • Biliary colic • Ureteric colic

Medical conditions which may mimic acute abdomen	
Referred pain Myocardial infarction Pneumonia	**Renal causes** Acute pyelonephritis Pelviureteric colic
Metabolic causes Diabetes ketoacidosis Acute intermittent porphyria Lead poisoining	**Hematological causes** Sickle cell crisis Polycythemia vera Hemophilia Henoch-Schonlein purpura
Functional gastrointestinal disorders Irritable bowel syndrome	**Vasculitis** Embolic

MECHANISMS OF ABDOMINAL PAIN

VISCERAL PAIN

- **Irritation or inflammation of peritoneum.**
  Peritonitis, pancreatitis.
- **Vascular insufficiency**
  Strangulation of bowel in hernia or volvulus, acute mesenteric vascular obstruction.
- **Spasm of hollow viscus**:
  Intestinal colic, biliary colic, ureteric colic
- **Stretching of capsule of solid organs**
  Liver, spleen & kidney when they become enlarged
- **Ulceration of tissue**
  Peptic ulcer

REFERRED PAIN

- **From the chest**
  Myocardial infarction, pleurisy
- **From the vertebral column**
  Nerve root compression, musculoskeletal disorders
- **From the gonads**
  Torsion of the testes

MISCELLANEOUS

- **Metabolic disorders:**
  Uremia, diabetes, porphyria, hypercalcemia, Addison's disease
- **Psychogenic disturbances**
  Irritable bowel syndrome

Localization of abdominal pain based on human observations	
Organ	*External localization on abdominal wall*
Stomach and duodenum	Epigastrium, midline or slightly to the right
Small intestine	Periumbilical or right iliac fossa
Transverse & sigmoid colon	Hypogastrium, midline
Right colon	Right lower quadrant
Left colon	Left lower quadrant
Rectosigmoid	Suprapubic
Bladder	Suprapubic
Rectum	Lower back, midline
Gallbladder	Mid-epigastric, radiating to Rt. upper quadrant and to Rt. scapular area
Common bile duct	Mid-epigastric, radiating to shoulders or retrosternally to neck
Pancreas	Mid-epigastric, spreading laterally to back if posterior peritoneum is involved.

DIAGNOSIS OF ACUTE ABDOMEN

Make your approach in a case of acute abdomen as following

History

1. Pain

- *Onset*: Sudden in perforated d uodenal ulcer & acute intestinal ishaemia while gradual in appendicitis.
- *Nature*: Colicky in intestinal obstruction, biliary colic & renal colic whereas continuous pain in peritonitis.
- *Other features:* Site, radiations, aggravating & relieving factors should also be asked.

2. Vomiting

It can occur in any acute abdominal pain but remains persistent in upper intestinal obstruction

Examination

Signs of peritonitis

- Tenderness
- Rebound tenderness
- Guarding – localized or generalized

Signs of obstruction

- Distension of abdomen due to gas
- Increased gut sounds (borborygmi)
- Absent gut sounds suggest peritonitis

Pelvic & rectal examination

- Pelvic examination for gynaecological disorders e.g. ruptured ectopic pregnancy
- Rectal examination to detect localized tenderness

Other observations

- *Tongue* – furred in most acute abdominal disease
- *Temperature* – fever more common in acute inflammatory conditions

Think of other conditions

- Diabetes mellitus (Ketoacidosis)
- Pneumonia (referred pain)
- Myocardial infarction (referred pain)
- Irritable bowel syndrome

INVESTIGATIONS

- *Blood count:* raised WBC in inflammatory conditions
- *Serum electrolytes*
- *Serum amylase:* high levels greater than 5- times normal indicate acute pancreatitis. Raised level below this can occur in any acute abdomen and should not be considered diagnostic of pancreatitis.
- *Urine analysis for:*
  Glucose & Ketones (for diabetic ketoacidosis)
  WBC – to exclude acute pyelonephritis
- Porphyrins – to detect porphyria
- *X-ray abdomen:* in erect and supine position to detect
  - Gas under the diaphragm (due to gut perforation)
  - Dilated loops of bowel or fluid level (due to intestinal obstruction)
  - Ultrasound to detect any abscess

ABDOMINAL DISTENSION

1. Fat
2. Flatus – (gaseous distension)
3. Fluid (ascites)
4. Fetus (pregnancy)
5. Full bladder
6. Feces

INTESTINAL OBSTRUCTION

Intestinal obstruction is a common surgical emergency and because of its serious nature it demands early diagnosis and speedy relief

TYPES

Simple or dynamic:
In this type there is peristalsis working against an obstructing agent which may be in the intestinal lumen, in the wall or outside the wall e.g. fecal impection, stricture and adhesions.

Strangulated or adynamic:
In this type peristalsis ceases and no propulsive wave occurs. It occurs when there is interference with the intestinal blood supply as when the bowel is trapped or twisted e.g. paralytic ileus or mesenteric vascular occlusion.

CLINICAL FEATURES

1. **Pain:**
   - Colicky pain in mechanical obstruction
   - Dull constant pain in paralytic ileus

2. **Vomiting**
   Copious – in high small bowel obstruction.
   Late or absent- in lower small bowel or colon.

3. **Abdominal distension**
   Distension may be confined to some loops of bowel which can be seen as ridges across the abdomen, forming ***"ladder pattern".*** Diffuse distension is late and may indicate chronic large bowel obstruction or paralytic ileus. In complete obstruction neither feces nor flatus is passed.

CAUSES OF INTESTINAL OBSTRUCTION

Luminal obstruction
Fecal impaction
Gallstone ileus
Worms e.g. ascariasis

Intrinsic lesions of the bowel wall
Tumors of large intestine
Strictures e.g. tuberculosis, Crohn's disease
Intussusception

Extrinsic compression
Adhesions
Hernias
Volvulus

Paralytic ileus
Peritonitis
Postoperative
Vascular

INVESTIGATIONS

- **Plain x-ray abdomen** (in erect and supine position)
  They show gaseous distension and fluid levels (ladder-like pattern)
- **Serum electrolytes**

DIFFERENTIAL DIAGNOSIS

- Pancreatitis
- Acute gastroenteritis
- Appendicitis

MANAGEMENT

1. Nothing by mouth
2. Decompression: by gastrointestinal drainage via a nasogastric tube.
3. IV fluids and electrolytes
   Antibiotics
5. **Conservative management** (non-surgical approach e.g. decompression IV fluids and antibiotics) for paralytic ileus and obstruction due to adhesions and postoperative obstruction.
6. **Urgent surgery:** for hernia, mechanical obstruction of large bowel and strangulation.

INTESTINAL PSEUDO- OBSTRUCTION

Intestinal pseudo- obstruction is an acute or chronic motility disorder characterized by distension or dilataion of small and large intestine. It presents with symptoms and signs of intestinal obstruction in the absence of any mechanical obstruction. In more than 80% of cases it complicates other clinical conditions (secondary pseudo-obstruction), in a few patient there is no underlying cause called idiopathic or primary pseudo-obstruction.

CHRONIC OR INTERMITTENT SECONDARY PSEUDO- OBSTRUCTION

Numerous medical conditions can cause chronic dilatation of large and small intestine such as following:

- Intra-abdominal sepsis
- Pneumonia
- Metabolic e.g electrolyte imbalance, diabetes mellitus, hypothyroidism.
- Neurologic conditions: Parkinson's disease, autonomic dysfunction, stroke.
- Drugs: opiates, antidepressants, anti-Parkinsonian drugs.
- Intra-abdominal trauma, pelvic spinal and femoral fractures.

Clinical features

Chronic or intermittent constipation, crampy abdominal pain, anorexia, and bloating. Gastric distension may be present.

Investigations

Abdominal x-ray shows gaseous distension of large and small bowel, air – fluid levels are unusual. Barium studies do not show tumor, stricture or volvulus (as there is no mechanical obstruction).

Management

- Metoclopramide (Maxolon) may help in diabetic patient.
- Discontinuation of anticholinergic drugs.
- Enemas to relieve fecal impaction.
- Regular use of stool softeners and high fiber diet.

ACUTE INTESTINAL PSEUDO -OBSTRUCTION

This condition is characterized by an acute intestinal dilatation involving primarily colon but occasionally also the small intestine.

This condition usually develops in patients who have major surgical or medical stress such as major surgery, myocardial infarction, sepsis or respiratory failure.

A number of patients are those on ventilators, have received narcotics or sedatives and have metabolic and electrolyte disturbances.

Clinical features

Clinical features are difficult to differentiate from mechanical obstruction. Patient complains of colicky lower abdominal pain and acute constipation.

Examination reveals distended abdomen with reduced bowel sounds. Local tenderness over the distended colon is common but diffuse abdominal tenderness, rigidity, or rebound tenderness are unusual.

Investigations

Abdominal x-ray shows massive dilatation of colon and small intestine, especially the cecum.

Management

- Correction of fluid and electrolyte abnormalities.
- Nasogastric tube for decompression.
- Avoidance of drugs that depress intestinal motility.
- Barium enema may be dangerous because of risk of perforating the already dilated bowel.
- Decompressive colonoscopy is beneficial in some patients and removal of cecum is required in some patients with massive dilatation.

<u>*Experience sharing*</u>

Acute pseudo- obstruction should be included in differential diagnosis in hospitalized patients complaining of abdominal pain and constipation. This topic is especially included in this edition because clinically we see this is not an uncommon condition and we have lost one old patient who was admitted with complete heart block, stayed for more than a week in the ward as a bedridden patient, complaining constipation and abdominal pain, diagnosis was delayed and patient died of intestinal rupture and shock.

ACUTE PANCREATITIS

Acute pancreatitis is a condition in which activated pancreatic enzymes leak into the substance of the pancreas and initiate the auto-digestion of the gland.

ETIOLOGY

In Pakistan most of the cases are associated with gallstones, while in the United States alcoholism is the major risk factor.

CAUSES OF ACUTE PANCREATITIS

Common (90%)

- Gallstones
- Alcohol
- Idiopathic

Rare

- Metabolic: hypercalcemia, hypertriglyceridemia
- Drugs: thiazide, azathioprine, sodium valporate
- Infection: mumps, Coxsackie virus
- Post – ERCP
- Trauma
- Organ transplantation
- Post surgical

PATHOPHYSIOLOGY

The pancreas secretes the digestive enzymes as proenzymes which are activated in the intestinal lumen. Acute pancreatitis may result when activation occurs in the pancreatic duct system or acinar cells. Exact pathogenesis is unknown, but may include edema or obstruction of the ampulla of Vater resulting in reflux of bile into pancreatic ducts or direct injury to the acinar cells. The pancreas shows edema and necrosis. The release of enzymes leads to fat necrosis both in the pancreas and in the peritoneal cavity.

CLINICAL FEATURES

There may be history of gallstones or alcoholism

Abdominal pain

- Sudden severe pain in epigastrium occurring often within 12-24 hours of a large meal or alcohol.
- The pain is usually persistent and radiates most frequently through to the back, to either shoulder or to one iliac fossa before spreading to involve the whole abdomen
- The pain usually is usually worse by walking and lying supine and better by sitting and leaning forward.

Nausea and vomiting

Nausea and vomiting are very common

Shock – in severe cases

On Abdominal Examination

- Tenderness in epigastrium
- Although severe pain, there may be little or no guarding of abdominal muscles at first. Later the upper abdomen becomes tender and rigid as peritoneal irritation increases.
- Mild abdominal distension – if paralytic ileus develops.
- Severe, advanced cases may develop bruising and discoloration in the left flank ***(Grey Turners Sign)*** and around the umbilicus (***Cullen's Sign)***. These are rare and late signs of extensive pancreatic destruction.

COMPLICATIONS

1. **Pancreatic abscess:** 2-5 weeks after onset
2. **Pancreatic pseudocyst:** 1-2 weeks after onset of acute pancreatitis present as a mass in upper abdomen, abdominal pain, nausea, vomiting and weight loss
3. **Pancreatic ascites:** due to disruption of pancreatic duct. Presents with abdominal pain and increase in girth.
4. **Shock and renal failure:** due to fluid loss into pancreas and surrounding tissues

ASSESSMENT OF SEVERITY

Ranson's criteria is generally used in assessing the severity of pancreatitis: Three or more of the following features on admission indicate severe disease.

1. Age > 55 years
2. Blood glucose > 200 mg/dl
3. WBC count > 16,000
4. AST > 250 IU/lit
5. Serum LDH > 350 IU/lit

Development of the following in the first 48 hours indicates a worsening prognosis.

1. Fall in hematocrit by > 10%
2. Fluid deficit of > 4 L
3. BUN rise > 5 mg / dl
4. Arterial PO2 < 60 mm Hg
5. Bicarb deficit > 4 meq/lit
6. Serum calcium < 8 mg / dl
7. Hypoalbuminemia (albumin < 3.2g/dl)

Mortality rate correlates with the number of criteria present:

Number of criteria	Mortality rate
0-2	1%
3-4	16%
5-6	40%
7-8	100%

COMPLICATIONS OF ACUTE PANCREATITIS

Complications	Causes and features
• Shock and renal failure	• Pancreatic necrosis is associated with leakage of fluid in the pancreatic bed, also ileus with fluid filled loops of bowel leading to pre- renal azotemia and then acute tubular necrosis.
• Hypoxia	• ARDS due to microthrombi in pulmonary vessels.
• Hyperglycemia	• Due to diruption of pancreatic islets.
• Hypocalcemia	• Sequestration of calcium in fat necrosis.
• Hypoalbuminemia	• Increased capillary permeability
Pancreatic	
• Necrosis	
• Abscess	• Rising fever, leukocytosis, localized tenderness and epigastric mass. It may be associated with left sided pleural effusion and enlarged spleen due to splenic vein thrombosis.
• Pseudocyst	Encapsulated fluid collection with high enzyme content. Usually less than 6cm sized pseudocysts resolve spontaneously. They may become secondarily infected requiring drainage of abscess.
• Ascites	• Gradual increase in abdominal girth and persistent elevation of serum amylase in the absence of frank abdominal pain. It results from rupture of pancreatic duct or drainage of pseudocyst into the pancreatic cavity
Gastrointestinal	
• Upper GI bleeding	• Gastric or duodenal erosion.
• Variceal hemorrhage	• Splenic or portal vein thrombosis
• Duodenal obstruction	• Compression by pancreatic mass.
• Obstructive jaundice	• Compressin of common bile duct

INVESTIGATIONS

Serum amylase

- Increased level of serum amylase 3-fold or more the normal value indicates acute pancreatitis, however other causes of elevated serum amylase should be excluded such as mumps and perforation or infarction of the intestine. It should be noted that serum amylase concentration has no prognostic value.
- Serum amylase becomes normal after 48-72 hours even with the continuing evidence of pancreatitis, therefore serum lipase should also be sent that remains elevated for 7-14 days.
- Persistently elevated serum amylase suggests development of pseudocyst, pancreatic abscess or non-pancreatic causes (e.g. intestinal obstruction, mumps, narcotics administration).

Serum lipase

Serum lipase remains elevated for 7-14 days. An elevated level of lipase is diagnostic of acute pancreatitis.

Other laboratory findings

- WBC – 15,000-30,000
- Glucose – High
- BUN – may be elevated
- Serum calcium – low in 25% of cases
- AST, bilirubin, alkaline phosphatase are transiently elevated. Serum albumin is low in 10% of patients and indicates severe pancreatitis.
- Markedly elevated LDH (>500U/dl) suggests poor prognosis.
- Serial assessment of C-reactive protein is a good indicator of progress.
- ABGs show hypoxia

Pain x-ray abdomen

It may show the following features:

- *Gall stones*
- *Sentinel loop:* a segment of air-filled small intestine in the left upper quadrant
- *Colon cut off sign:* a gas-filled segment of transverse colon abruptly ending at the area of pancreatic inflammation
- Features of paralytic ileus
- Left pleural effusion or collapse of lung

CT Scan

- It is diagnostic even in the presence of normal serum amylase.
- It is useful in detecting enlarged pancreas, pseudocyst, abscess and hemorrhage into and around pancreas
- The presence of gas bubbles on CT scan indicates pancreatic abscess

Ultrasound

It is used to detect gallstones and biliary obstruction and serial assessment of pseudocysts, although in the earlier stages the gland may not be grossly swollen and may be missed on ultrasound.

DIFERENTIAL DIAGNOSIS

- Perforated peptic ulcer
- Acute cholecystitis and biliary colic
- Acute intestinal obstruction
- Renal colic
- Myocardial infarction
- Vasculitis
- Pneumonia
- Diabetic ketoacidosis

MANAGEMENT

In most patients acute pancreatitis is a mild disease that subsides spontaneously within several days. The pancreatic rest program includes withholding food and liquids by mouth, bed rest and in patients with severe pain and ileus nasogastric suction by N/G tube.

Supportive Treatment

1. Bed rest, nothing by mouth (NPO)
2. IV fluids: saline, or whole blood according to the need.
3. Nasogastric suction: if severe nausea, vomiting or development of paralytic ileus.
4. Pethidine 3-4 hourly to control pain. (Avoid morphine which can cause spasm of sphincter of Oddi)
5. Oxygen for hypoxia, ventilator may be required for patients with ARDS.
6. Dopamine may be required if shock does not respond to fluid replacement.
7. Calcium gluconote IV only if hypocalcemia is associated with tetany.
8. Fresh frozen plasma for coagulopathy

9. Serum albumin for hypoalbuminemia.
10. Insulin for hyperglycemia.
11. Total parenteral nutrition if there is severe pancreatitis and ileus for 7-10 days.

12. ***Antibiotics*** : prophylactic broad spectrum antibiotic is given even in sterile pancreatitis to prevent infection.

- Imipenem (Inj. Tinenam) 500mg IV 8- hourly (expensive but very effective) OR
- Cefuroxime (Inj. Zinacef) 1.5g IV 8-hourly.

13. ***ERCP***

- When severe pancreatitis results from stone in biliary tract; particularly if there is jaundice or cholangitis ERCP with endoscopic sphicterotomy and stone extraction is indicated.

Treatment of pseudocyst

With prolonged bowel rest (by NPO) and parenteral nutrition many pseudocysts resolve spontaneously. If it does not resolve after 4-6 weeks surgical drainage is necessary.

Surgery

- Surgical opinion is necessary in all cases of severe pancreatitis.
- Surgery is necessary for abscess, persistent pseudocyst and severe hemorrhagic pancreatitis (causing ascites).the goal of surgery is to debride necrotic pancreas and surrounding tissue and establish adequate drainage.

MANAGEMENT OF ACUTE PANCREATITIS

- Bed rest
- NPO
- Intravenous fluid
- Oxygen
- Pethidine
- Antibiotics
- Parenteral nutrition
- Dopamine
- Calcium gluconate
- Fresh frozen plasma, whole blood
- Insulin
- Albumin
- ERCP
- Surgery

CHRONIC PANCREATITIS

Chronic pancreatitis is a chronic inflammatory disease characterized by fibrosis and destruction of exocrine pancreatic tissue. Diabetes mellitus occurs in advanced cases.

Etiology

Tropical pancreatitis related to malnutrition is a common cause in developing countries while alcoholism is the main reason in Western countries. Other causes are stenosis of ampulla of Vater, cystic fibrosis, hereditary and idiopathic.

Clinical features

- All patients present with abdominal pain. In about 50% of cases this occurs as episodes of acute pancreatitis with some permanent pancreatic damage, in some patients it presents slowly progressively without acute exacerbation and in a few some patients it presents with diarrhea without abdominal pain.
- Weight loss is common and results from anorexia, avoidance of food because of post- prandial pain, malabsorption and/ or diabetes.
- Steatorrhea occurs when more than 90% of exocrine tissue has been destroyed. About 30% patients become diabetic.
- On examination patient is wasted with epigastric tenderness.

Complications

- Pseudocys
- Pancreatic ascites
- Obstructive jaundice
- Duodenal stenosis
- Portal or splenic vein thrombosis
- Peptic ulcer

Investigations

- Plain abdominal x-ray shows calcified pancreas
- Ultrasound abdomen
- CT abdomen: may show atrophy, calcification.
- ERCP: if non-invasive tests are negative or equivocal.
- Endoscopic ultrasound

Management

- Pain relief: NSAIDS, opiates.
- Oral pancreatic enzyme supplements
- Endoscopic therapy: dilatation or stenting of main pancreatic duct, removal of stones.
- Surgical therapy: partial pancreatic resection, pancreato- jejunostomy.

CARCINOMA OF PANCREAS

INCIDENCE

- Adenocarcinoma is the most common malignancy of pancreas (90%)
- 70% of adenocarcinoma occurs in the head of pancreas, 30% in body or tail.
- Men are more affected, peak age 55-65 years

ETIOLOGY

- Long term exposure to DDT
- Smoking
- Chronic pancreatitis

CLINICAL FEATURES

1. **Abdominal pain:** Postprandial epigastric or periumbilical pain which radiates to the back, relieved by sitting up or bending both knees and exaggerated by eating
2. **Anorexia, nausea and weight loss**
3. **Jaundice:** In majority of cases with involvement head of pancreas, painless and progressive jaundice is the presenting complaint (obstructive jaundice)
4. **Diarrhea and steatorrhoea also common**
5. **Courvoisier's sign:** palpable gall bladder in a jaundiced patient is usually the consequence of distal biliary obstruction by a pancreatic cancer.
6. **Epigastric mass:** palpable epigastric mass may be found on physical examination

INVESTIGATION

Laboratory Findings

- LFTs show obstructive jaundice. Raised serum alkaline phosphate due to hepatic metastasis or compression of common bile duct
- Hyperglycemia or true diabetes in 10-20% of cases.
- CA 19-9, a tumor. marker – associated with carcinoma pancreas has sensitivity of 70% and specificity of 87%. It is also elevated in acute and chronic pancreatitis and cholangitis.

Imaging

- Diagnosis is usually made by CT scan or MRI
- Ultrasound is not reliable due to interference by intestinal gas.
- Contrast CT or MRI: show mass in 75-80% of patients, allow getting percutaneous fine –needle aspiration biopsy.
- Barium meal: reveals a widened loop or an inverted '3' sign due to indentation of the pancreas along the medial aspect of the duodenum
- ERCP is helpful when diagnosis is in doubt. Stent can be inserted in common bile duct through ERCP to relieve obstructive jaundice

MANAGEMENT

Surgery:

Curative surgery:

Curative surgery is possible in patients with cancer limited to head of pancreas. Only 15% cases are candidates for curative surgery. The procedure is called "*Whipple's procedure*" (resection of the pancreas with excision of the common bile duct and duodenum). Surgical mortality is high.

Palliative surgery

In majority of patients only palliative surgery is considered to relieve or prevent obstructive jaundice by anastomosing the gallbladder to the jejunum.

Combined radiotherapy and chemotherapy

May be used for palliation of unresectable cancer confined to the pancreas

Relief of pain

Methadone or morphine

PROGNOSIS

Very poor

ACUTE APPENDICITIS

Appendicitis is the most common abdominal surgical emergency. It occurs most commonly in ages group of 10-30 years. It is initiated by obstruction of the appendix by fecalith, inflammation, foreign body or neoplasm. Obstruction leads to increased intraluminal pressure, venous congestion, infection and thrombosis of vessels. If untreated, gangrene and perforation may develop within 36 hours.

CLINICAL FEATURES

SYMPTOMS

1. **Pain:** It begins as a vague, central abdominal pain (around the umbilicus or epigastrium) and shifts to the right iliac fossa within a few hours.
2. **Anorexia:** Preceding the pain
3. **Nausea & Vomiting:** Vomiting is not so frequent
4. **Constipation or diarrhea:** Mostly patients with appendicitis develop constipation for a few days before the attack of the pain. A few patients have diarrhea.

SIGNS

1. Fever: low grade fever (100 F)
2. White & furred tongue
3. Tenderness in right iliac fossa
4. Localized guarding over the inflamed appendix

Confirmatory signs

1. ***Rovsing's sign:*** Pressure on the left iliac fossa produces pain on the right iliac fossa
2. ***Psoas's sign:*** Pain on extension of right thigh with the patient lying on the left side
3. ***Obturator's sign:*** Pain on internal rotation of the flexed right thigh while the patient lying in supine position
4. ***Rebound tenderness:*** Tenderness in the right iliac fossa after releasing pressure
5. ***Rectal examinations:*** may demonstrate, tenderness in the pelvis

INVESTIGATIONS

Blood CP:
Blood CP shows leucocytosis (10,000-20,000) with neutrophilia.

Ultrasound abdomen
Ultrasound has diagnostic accuracy of over 85%, but it is not performed if clinical diagnosis is strong. CT scan can be done in suspected perforated appendix to diagnose periappendicular abscess.

TREATMENT

Appendicectomy

ACUTE CHOLECYSTITIS

Acute inflammation of the gall bladder (cholecystitis) is associated with gallstones in over 90% of cases. It occurs when a stone becomes impacted in the cystic duct and inflammation develops behind the obstruction due to stasis and secondary infection. Infecting organisms are E. coli, klebsiella, streptococcus fecalis & anaerobes.

CLINICAL FEATURES

1. Pain
   - **Onset:** It may be sudden in onset or superimposed on the pain of chronic cholecystitis, usually precipitated by large or fatty meal.
   - **Site:** Epigastrium or right hypochondrium
   - **Radiation:** It radiates through the trunk to the tip of t he right scapula
   - **Aggravating factors:** Movement and breathing
   - **Relieving factors:** No, except analgesics
2. **Nausea and vomiting in 75% of cases**
3. **Loss of appetite**

EXAMINATIONS

- Patient anxious, lying quietly with shallow breathing
- Tachycardia 90-100 beats/min
- Fever (100-102 F), there may be rigors

- Tenderness and guarding in the right hypochondrium
- In severe cases there may be palpable inflammatory mass around the gall bladder
- Boas's Sign: The area of skin below the scapula at 9, 10, 11 rib becomes hypersensitive (hyperesthesia). It is called Boas's Sign.
- Jaundice is present in 25% of cases.

INVESTIGATIONS

1. **Blood CP:** TLC is usually high (12,000-15,000).
2. **LFTS:** raised serum ALT, AST, and alkaline phosphatase.
3. **Ultrasound:** shows gallstones, it is not specific for acute cholecystitis (67% sensitivity, 85% specificity).
4. **HIDA Scan**: indicates cystic duct obstruction.

DIFFERENTIAL DIAGNOSIS

- Perforated peptic ulcer
- Acute pancreatitis
- Appendicitis
- Perforated colonic carcinoma
- Liver abscess
- Hepatitis
- Basal pneumonia with pleurisy.

COMPLICATIONS

Gangrene of gallbladder
Progression of right upper quadrant pain, tenderness, guarding, fever and leukocytosis after 24-48 hours suggests possibility of gangrene of gallbladder.

Cholangitis
Cholangitis manifests as fever, jaundice and right hypochondrial pain.

Chronic cholecystitis
Chronic cholecystitis may develop with repeated episodes of acute cholecystitis.

TREATMENT

Medical management
Conservative or medical management consists of 3A (Aspiration, Analgesics, and Antibiotics)

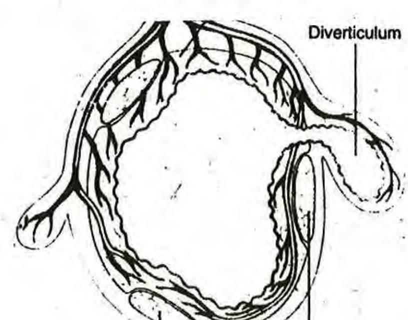
- Nasogastric aspiration and intravenous fluids
- Analgesics e.g pentazocine (Inj. Sosegon)
- Antibiotics
  - Inj. Cefuroxime (Zinacef) 1.5 g IV 8-hourly + Inj. Metronidazole 500mg 8 hourly

Surgical management

- Cholecystectomy: early cholecystectomy is now trend because there is no technical complications with early surgery. Laproscopic cholecystectomy is performed within 2-3 days after hospitalization.
- In high-risk patient, ultrasound guided aspiration of gallbladder may postpone or even avoid the need for surgery. Cholecystectomy is mandatory when there is evidence of gangrene or perforation.

DIVERTICULAR DISEASE

The diverticula are outpouchings that can occur throughout the GIT but most common in colon of middle-aged or in elderly
The presence of diverticula is known as diverticulosis
Inflammation of diverticula is called diverticulitis



Etiology

Raised intracolonic pressure due to low fecal residue resulting from low fiber diet is the suggested cause of diverticula formation. High fiber diet produces high fecal residue that produces low intracolonic pressure and therefore protects from the disease

Pathology

- Pelvic colon is most commonly involved
- Diverticulitis results from presence of a fecolith in diverticulum. The feces collect because of the inability of the diverticulum to contract. This fecal retention produces local inflammation in diverticula.

Clinical Features

- Diverticular disease is asymptomatic in 90% of the patients. No treatment required for asymptomatic cases. It may present with pain in left iliac fossa. Sometimes associated with constipation or passage of frequent loose stools
- Acute diverticulitis presents with:
  - Severe pain in left iliac fossa
  - Fever and constipation
  - On examination there is tenderness guarding and rigidity on left side of the abdomen

Complications

1. Abscess formation
2. Perforation
3. Fistula formation into bladder, vagina
4. Intestinal obstruction
5. Rectal bleeding

Investigations

- Sigmoidoscopy
- Barium enema

Management

1. ***For asymptomatic cases:***
   - No specific treatment
   - High fiber diet
   - Bulk laxatives e.g. methylcellulose
2. ***During acute attack of diverticulitis***
   - NPO. Bed rest
   - Metronidazole
   - I/V fluid
3. ***Surgery***
   - If uncontrolled by medical treatment
   - Local resection (Partial colectomy) with primary anastomosis

MEGACOLON

It is a collection characterized by dilatation of the colon and obstinate constipation. It may be congenital or acquired. Hirschsprung's disease is the congenital cause of megacolon in which there is congenital absence of the myenteric nerve plexus in the wall of the pelvic colon and upper rectum.

Symptoms:

Symptoms of colonic obstruction (constipation, vomiting, abdominal distension), usually late from birth but in few cases this condition may present in childhood.

Signs:

Persistent abdominal swelling

Investigations:

1. Barium enema shows:
   Small rectum, narrow segment above and then wide dilatation of colon, full of retained feces

2. Rectal biopsy shows
   Absence of ganglion

Treatment:

Excision of the abnormal segment of colon and rectum

MECKEL'S DIVERTICULUM

It is remnant of the vitelline duct that occurs in about 2% of the population occurring on the antimesenteric border of the ileum about 50cm from the ileocecal value. It may contain gastric mucosa which may secrete acid to cause mucosal ulceration and bleeding. It may cause obstruction or inflammation and so present like an acute appendicitis.

COMMONLY USED DRUGS IN GASTROENTEROLOGY

Following are the commonly used brands of drugs. Pharmaceutical companies are invited for advertisement of their products.

T: tablet, C: capsule, I: injection, S: syrup

H2 – BLOCKERS

Famotidine
T. Pepcidine 40mg MSD
T. Polypep 20, 40mg Wilson
T. Nocid 20, 40mg Novartis
T. H2F 20, 40mg Ferozsons
T. Peptiban 20, 40mg Werrick
T. Optifam 20, 40mg Merck

Ranitidine
T. Zantac 150, 300mg GlaxoSmithKline
I. Zantac 50mg IM, IV
T. Ranax 150, 300mg Standpharm
T. Peptinil 150, 300mg DS, Wilson
S. Peptinil Wilson

Cimitidine
T. Tagamet 200, 400mg
I. Tagamet IM, IV

PROTON PUMP INHIBITORS (PPI)

Omeprazole
C. Losec 20mg Barrett Hodgson
I. Losec 40mg IV infusion diluted in 100cc / 1hr
C. Zoltar 20mg PharmEvo
C. Encid 20, 40mg Wison
C. Meprazole 20, 40mg Werrick
C. Omega 20mg Ferozsons
C. Risek 20mg Getz Pharma
C. Sante 20mg Macter

Lansoprazol
C. Zoton 30mg Wyeth- Lederle
C. Inhibitol 30mg Highnoon
C. Lanzit 30mg Medinex
C. Lanzol 30mg Pharmatec

Pentaprazole
T. Protium 40mg Knoll

ANTACIDS

T.& S. Gaviscon Reckett

T & S. Gelusil Parke- Devis

T & S. Mucaine Wyeth – Ledrle

T & S. Mylanta 2 Parke- Devis

T & S. Simeco Wyeth- Lederle

T & S. Wydrate plus Wyeth- Lederle

S. Philips Milk of Magnesia Glaxosmithkline

S. Polycrol forte gel Reckitt Benckiser

T. Trisil Efroz

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This space is reserved for doctors, technicians, hospitals and laboratories for advertisement of their medical and surgical procedures and diagnostic facilities. Please contact the author with your name, qualification, procedure or diagnostic tool and laboratory investigations with address and charges.

- **Ultrasound:** upper abdomen, pelvis, whole abdomen.
- **Endoscopy**: upper and lower GI endoscopy, sclerotherapy, banding.
- **CT scan**: abdomen, pelvis. CT guided biopsy
- Liver biopsy
- Peritoneal biopsy
- X- ray abdomen
- **Barium studies**: barium swallow, barium meal, barium follow through, barium small bowel enema, barium enema.
- **Surgical procedures** especially laproscopic surgery.
- **Oncologists**: peoples have very little knowledge about good oncologists and hematologist.

LIVER & BILIARY SYSTEM 3

NORMAL LIVER FUNCTIONS

Recognition of normal liver functions is necessary to understand the manifestations that develop when the liver becomes abnormal due to disease process.

SYNTHETIC FUNCTION

Protein synthesis

Liver is the principal site of synthesis of all circulating proteins except gamma- globulins, which are produced in the reticuloendothelial system. Plasma contains 6-8 mg/dl of proteins, mainly in the form of albumin, globulin and fibrinogen. Liver also synthesizes complement factors, transferin, haptoglobin, caeruloplasmin, protease inhibitors (α 1-antitrypsin), and α-fetoprotein.

Albumin has half-life of 16-24 days and 10-12g is synthesized daily. Its main functions are to maintain the intravascular colloid osmotic pressure and to transfer water-insoluble substances such as bilirubin, hormone, fatty acids and drugs.

- Albumin synthesis is reduced in chronic liver disease and malnutrition. It can be lost in nephrotic syndrome and in protein – losing enterpathy.
- Hypoalbuminemia results in edema.

Coagulation proteins

Liver also synthesizes all coagulation factors (other than factor VIII) such as fibrinogen, prothrombin, factors V, VII, IX, X and XII.

- Deficiency of coagulation factors results in bleeding tendency.

METABOLIC FUNCTIONS

Carbohydrate metabolism

Liver is the main source of plasma glucose as it is the main body storage site for glycogen. In the fasting state glucose is derived from breakdown of glycogen (glycogenolysis) and gluconeogenesis (formation of glucose from amino acids and fatty acids).

- Liver damage can lead to hypoglycemia.

Fat metabolism

Liver synthesizes triglycerides, cholesterol, phospholipids and lipoproteins.

Protein metabolism

In addition to its synthetic function, liver is the central organ in protein catabolism and synthesis of urea formation. Ammonia is produced by the degradation of amino acids that is converted into urea. Urea is secreted by the liver into plasma for excretion by the kidney. This is the major pathway for the elimination of nitrogenous waste.

- Ammonia level becomes high in severe liver disease that is harmful for brain and may lead to hepatic encephalopathy.

EXCRETORY FUNCTION

Liver is responsible for excretion of many substances in the bile.

Bilirubin metabolism

Bilirubin is produced mainly from the breakdown of mature red cells in Kuffer cells of the liver and in the reticuloendothelial system. Biliverdin is formed from haem after removal of iron; this biliverdin is reduced to form bilirubin. The bilirubin produced is unconjugated and water-insoluble, and is transported to the liver attached to albumin. Bilirubin dissociates from albumin and is taken up by the hepatic cells, where it is conjugated with glucuronic acid and is excreted in bile.

- In liver disease there may be obstruction to excretion of bilirubin manifesting as jaundice.

This conjugated bilirubin enters in intestine within bile, and is not absorbed because of its large molecular size in the terminal ileum. Bacterial enzymes hydrolyze the molecule, releasing free bilirubin, which is then reduced to urobilinogen. Some of this is excreted in the stools as stercobilinogen and the remainder is absorbed by the terminal ileum, passes to the liver via enterohapatic circulation and is re-excreted in bile. Urobilinogen bound to albumin enters the circulation and is excreted in the urine via kidneys.

Bile acids metabolism

Bile acids are synthesized in hepatocytes from cholesterol. They are excreted in bile and then pass into the duodenum. Bile acids are detergents, causing fat solubilization that is necessary for absorption of lipids and lipid-soluble vitamins such as vitamin A, D, E and K.

- Decreased excretion of bile salts in liver disease causes:
  - Pruritus (itching)
  - Bleeding disorder: deficiency of vitamins such as vitamin K leads to decreased formation of vitamin K dependent coagulation factors resulting in bleeding tendency.
  - Steatorrhea (fatty stool) due to fat malabsorption.

DETOXIFICATION FUNCTION

Liver plays a vital role in detoxifying nitrogenous compounds derived from intestine, as well as many hormones, drugs and chemicals.

Normal and abnormal liver functions

Liver function	Abnormality	Manifestation
Albumin synthesis	Hypoalbuminemia	Edema
Synthesis of coagulation proteins	Deficiency of coagulation proteins	Bleeding, prolonged PT
Glycogen storage	Hypoglycemia	Brain damage
Bile acid formation	Decreased excretion	Steatorrhea, deficiency of fat soluble vitamins
Bilirubin excretion	Hyperbilirubinemia	Jaundice
Excretion of nitrogenous substances	Increased serum ammonia	Hepatic encephalopathy
Inactivation of drugs	Increased drug level duration	Toxicity
Hormone catabolism	Increased level of insulin, glucagons, estrogen, growth hormone, glucocorticoids and parathyroid hormone	Gynaecomastia and other effects

LIVER FUNCTION TESTS (LFTs)

The term "Liver function tests" (LFTs) refers to a group of biochemical investigations useful in confirming :

- Liver diseases
- Whether hepatic cells or biliary tree is involved
- What is the extent of liver damage.

Following tests are required to assess the liver functions:

1. Serum bilirubin
2. Hepatic enzymes SGOT(AST), SGPT(ALT), alkaline phosphatase.
3. Prothrombin time (PT)
4. Serum proteins with albumin and globulin ratio (A/G ratio).

Clinical laboratories usually perform serum bilirubin and liver enzymes when only LFT is requested. Serum proteins and PT are requested separately (PT requires specific PT bottle).

SERUM BILIRUBIN

Normal serum bilirubin level is less than 1mg/dl with direct or conjugated bilirubin less than 0.25mg/dl. Jaundice is usually visible in the sclera or skin when serum bilirubin exceeds 2.5 mg/dl

Predominantly indirect or unconjugated hyperbilirubinemia:

Indirect hyperbilirubinemia may result from impaired conjugation due to:

- Increased bilirubin production due to hemolysis as in malaria and hemolytic anemias.
- Defective hepatic uptake of bilirubin in Gilbert's syndrome.
- Impaired bilirubin conjugation in Gilbert's syndrome, Crigler- Najjar syndrome, neonatal or physiological jaundice.

Predominantly direct or conjugated hyperbilirubinemia

Direct hyperbiliribunemia develops as a result of:

- Intrahepatic obstruction to bile flow (intrahepatic cholestasis) due to viral hepatitis, alcoholic liver disease, sepsis, biliary cirrhosis, pregnancy and drugs such as oral contraceptives and androgens.
- Extrahepatic obstruction to bile flow (extrahepatic cholestasis) due to gall stones obstructing the biliary tree, carcinoma of head of pancreas and biliary strictures.

HEPATIC ENZYMES

In liver cells many enzymes are present which may be released into the blood when liver cells are damaged or killed. Measurement of the activity of these enzymes in the blood may give evidence of hepatocellular disease.

Aminotransferases:

Alanine aminotransferase ALT
(Formerly called as serum glutamic pyruvic transaminase (SGPT).

Aspartate aminotransferase AST
(formerly called as serum glutamic oxaloacetic transaminase (SGOT).

- ALT is found primarily in the liver, therefore it is more specific to liver disease than AST that is also present in heart, skeletal muscle, kidney and brain, and therefore AST is elevated also in myocardial infarction and skeletal muscle disorders while the ALT rises only in liver disease.
- The source of serum ALT and AST in a normal person is unclear.
- Normal level of AST or ALT is less than 35U/L.
- AST level twice that of ALT is typical of alcoholic hepatitis.
- These enzymes are slightly high in obstructive jaundice & very high enzymes in hepatocellular damage.
- Absolute levels of aminotransferases do not correlate with the severity of liver injury or prognosis. Thus in the patient with massive hepatic damage there will be marked elevation of aminotransferases (in thousands) during the early phase (24-48 hours), but by the time patient is tested 3-5 days later, the levels may be in the range of moderate elevation (200-350 U/L.)

Alkaline phosphatase
Alkaline phosphatase is present in the canalicular and sinusoidal membranes of the liver and is raised in the following conditions:

- Hepatocellular disease: When hepatocytes are damaged, little alkaline phosphatase is liberated into the blood from cells which are killed. As a result, plasma alkaline phosphatase activity rises but not more than twofold in acute or chronic hepatocellular disease.
- Obstructive jaundice: Very high level of this enzyme which may be 4-6 times the normal limit occurs in obstructive jaundice.
- Infiltration of the liver (e.g. metastasis).
- Cirrhosis even in the absence of jaundice.
- Primary biliary cirrhosis.

Alkaline phosphatase is also present in intestine, bone & placenta, therefore it increases also in the diseases of the above structures. To confirm its origin from liver, another enzyme called Gamma GT is also measured simultaneously that is also elevated alongwith raised alkaline phosphatase if source is liver because both are liberated from hepatobiliary system.

Gamma-Glutamyl Transferase (γ-GT)
Gamma GT is present in hepatobiliary system and in other tissues. In liver disease its level correlates with the level of alkaline phosphatase. It is the most sensitive indicator of biliary tract disease. However it can elevate in pancreatitis, cardiac, renal and pulmonary disorders as well as in diabetes, alcoholism and with certain drugs.

- Moderately increased level occurs in acute parenchymal damage.
- The highest increase occurs in biliary obstruction.

LIVER FUNCTION TESTS LABORATORY VALUES			
Tests	Normal values	Hepatocellular jaundice	Obstructive jaundice
Bilirubin			
Direct	0.1- 0. 3mg/dl	Increased	Increased
Indirect	0.1- 0.7 mg/dl	Increased	Increased
Urine bilirubin	None	Increased	Increased
AST ALT	5-40 units/L 5-30 units/L	Increased in hepatocellular damage, viral hepatitis	Minimally increased
Alkaline phosphatase	30-115 units/L	Increased +	Increased ++++
PT INR APTT	8-10.5 sec 1-1.4 26-37 sec	Prolonged if damage is severe; not responding to vitamin K	Prolonged if obstruction is marked; but responding to vitamin K
Serum albumin Total protein	3.6- 4.7 g/dl 6-8 g/dl	Albumin decreased	Unchanged

PROTHROMBIN TIME (PT)

Prothrombin time increases as a result of severe acute or chronic liver damage leading to impaired synthesis of the clotting factors which are vitamin-K dependent (V, VII, X). Therefore prothrombin time is dependent on normal hepatic synthesis of clotting factors and sufficient intestinal uptake of vitamin K. Severe acute or chronic hepatic parenchymal injury may lead to prolongation of PT due to impaired synthesis of clotting factors. Clotting factors have short half-life than albumin therefore prothrombin time prolongs earlier than hypoalbuminemia in severe liver injury.

PT is usually not prolonged in acute hepatitis; but if it is prolonged that indicates extensive hepatocellular necrosis and reflects a worse prognosis.

APTT

Activated partial thromboplastin time (APTT) which reflects the activity of fibrinogen (factor I), prothrombin (factor II) and factors V, VIII, IX, X, XI, and XII may also be prolonged in severe liver disease.

PLASMA PROTEINS

Albumin is synthesized entirely in the liver. In chronic liver disease, especially in cirrhosis the liver function reduces and the serum albumin concentration becomes low. Normal value is 3.5-5.5 mg/dl (Other causes of low albumin are malnutrition, nephrotic syndrome and protein losing enteropathy).

Globulin: high globulin and low albumin is a characteristic feature of chronic liver disease. Normal value ranges from 2-3.5mg/dl. Hyperglobinemia may be due to some immunological mechanism. 1gG increases in chronic liver disease, 1gA increases in alcoholic liver disease and 1gM increases in primary biliary cirrhosis.

Liver function tests used to assess liver disease		
Measurement	***Fluid***	***Assessment***
Bilirubin	Plasma or urine	Transport
Aminotransferases	Plasma	Hepatocellular damage
Alkaline phosphatase	Plasma	Biliary obstruction
Gamma-glutamyl transferase	Plasma	Enzyme induction
Proteins (total and albumin)	Plasma	Synthesis
PT, APTT	Plasma	Synthesis

LIVER BIOPSY

INDICATIONS

1. Chronic hepatitis – for diagnosis, grading and staging.
2. Unexplained hepatomegaly or hepatosplenomegaly.
3. Cirrhosis: for diagnosis and detection of the cause such as alcohol abuse, hepatitis B, hemachromatosis, alpha- 1 antitrypsin deficiency.
4. Tumors – primary and secondary.
5. Drug related liver disease
6. Alcoholic liver disease
7. Cholestasis of uncertain cause
8. Persistently abnormal liver function tests
9. Suspected systemic or infiltrative diseases such as sarcoidosis, military tuberculosis or fever of unknown origin.

CONTRAINDICATIONS

1. Uncooperative patient
2. Prolonged prothrombin time (PT) by 3 seconds or more over control.
3. Platelets less than 80,000/mm^3/liter
4. Gross ascites because there is risk of continued leakage of ascitic fluid.
5. Severe hepatocellular failure
6. Passive congestion of liver (e.g. in cardiac failure).
7. Infection of the right pleural space and cholangitis.
8. If there is possibility of hydrated cyst.
9. Suspected vascular lesion (hemangioma).

If the ***percutaneous*** biopsy is contraindicated due to bleeding disorder or ascites, biopsy can be carried out by ***transjugular*** approach, in which the tissue is obtained via the hepatic vein and any bleeding occurs directly into the vascular space.

PRECAUTIONS:

- Any history of bleeding should be investigated.
- Blood group should be known, and transfusion facilities should be available.
- Hemoglobin should be more than 10g/dl.
- Platelet count more than 80,000/mm^3
- PT should not be prolonged more than 3 seconds.

PROCEDURE OF LIVER BIOPSY

- This should be performed only by experienced doctors and with sterile precautions.
- The patient's coagulation status (prothrombin time, platelets) is checked.
- The patient's blood group is checked and serum saved for cross matching.
- The patient lies on his back at the edge of the bed.
- The liver margins are delineated using percussion.
- Local anaesthetic is injected at the point of maximum dullness in the mid-axillary line through the intercostals space during expiration. Anesthetic (1% lignocaine, approximately 5 ml) should be injected down to the liver capsule.
- A tiny cut is made in the skin with a scalpel blade.
- A special needle (**Trucut**) is used to obtain the liver biopsy whilst the patient holds his breath in expiration.
- The biopsy is laid on filter paper and placed in 10% formation. If a culture of the biopsy is required it should be placed in a sterile pot.
- The patient lies on right side for 2 hours and should be observed with pulse and blood pressure measurements taken regularly for 6 hours.

COMPLICATIONS OF LIVER BIOPSY

1. Pain (0.056-22%)
   - Pleuritic
   - Peritoneal
   - Diaphragmatic
2. Hemorrhage
   - Intraperitoneal
   - Intrahepatic and/or subcapsular
   - Hemobilia
3. Bile peritonitis
4. Bacteremia
5. Sepsis (0.088%) and abscess formation
6. Pneumothorax and/or pleural effusion
7. Hemothorax
8. Arteriovenous fistula
9. Subcutaneous emphysema
10. Anesthetic reaction
11. Needle break
12. Biopsy of other organs
    - Lung
    - Gallbladder
    - Kidney
    - Colon
13. Mortality (0.0088-0.3%)

SIGNS & SYMPTOMS OF LIVER DISEASE

ACUTE LIVER DISEASE

Symptoms

- Anorexia
- Malaise
- Fever
- Jaundice

Signs

- Jaundice
- Hepatomegaly
- Pale stool and dark colored urine

CHRONIC LIVER DISEASE (CLD)

Symptoms

1. Right hypochondrial pain due to stretching of liver capsule as a result of hepatomegaly.
2. Ankle swelling due to fluid retention.
3. Gynaecomastia (enlargement of male breast), loss of libido and amenorrhea due to endocrine dysfunction
4. Pruritus due to cholestasis, this is often an early symptoms of primary biliary cirrhosis.
5. Hematemasis and melena from GIT hemorrhage
6. Confusion and drowsiness due to neurological complication (hepatic encgphalopathy).

Signs:

Skin

- Palmar erythema indicating hyperdynamic circulation. (may also occur in pregnancy, thyrotoxicosis, rheumatoid arthritis, CO_2 retention and old age).
- Clubbing occasionally occur.
- Dupuytren's contracture (often in alcoholic cirrhosis).
- Spider nevi: these are telangiectasias that consist of a central arteriole with radiating small vessels. They are found in the distribution of the superior vena cava (i.e. above the nipple line).
- Jaundice

Abdomen

- Initial hepatomegaly followed by small liver in well established cirrhosis.
- Splenomegaly – indicating portal hypertension.

Endocrine system

- Testicular atrophy
- Gynecomastia: enlargement of male breast occurs due to decreased estrogen metabolism in diseased liver, it also results from treatment with spironolactone, a diuretic commonly used for edema and ascites in cirrhosis.

With complications

- Jaundice
- Encephalopathy: (drowsiness, stupor, flapping tremor of outstretched hands, and fetor hepaticus).
- Collateral veins e.g. veins around the umbilicus forming *caput medusae*
- Peripheral edema
- Ascites.

HOW TO EXAMINE PATIENT OF CLD

Sequence of examination in chronic liver disease (ranging from chronic hepatitis to cirrhosis of liver) should be as following:

Hand
- Clubbing, leuconychia
- Pallor, palmar erythema, Dupuytren's contractures, flapping tremor.
- Spider nevi, scratch marks (due to pruritus) generalized pigmentation.

Eyes and face
- Jaundice, cyanosis,
- Parotid enlargement.

Chest
- Spider nevi
- Loss of axillary hair
- Gynecomastia.

Abdomen
- Splenomegaly, Hepatomegaly
- Ascites

Legs
- Pedal edema

ACUTE LIVER DISEASE

CAUSES

1. Viral infections
- Hepatitis virus A, B, C, D, E
- Epstein – Barr virus
- Cytomegalovirus
- Yellow fever virus

2. Non-viral infections
- Leptospira
- Toxoplasma gondi
- Q fever

3. Poisons
- Aflatoxin
- Carbon tetrachloride
- Mushrooms

4. Drugs
- Paracetamol
- Halothane

5. Alcohol

6. Other
- Pregnancy
- Shock
- Wilson disease

VIRAL HEPATITIS

HEPATITIS A

1. This is the most common type of viral hepatitis, highly infectious and is caused by hepatitis A virus. This disease commonly affects children and young adults.
2. Spread of infection is mainly by the oro-fecal route and arises from the ingestion of contaminated water and food (e.g. milk). Overcrowding and poor sanitation facilitate the spread. Infected person excretes virus in the feces for about 2 weeks before the onset of clinical illness and for up to 7 days after.
3. Hepatitis A is maximally infectious just before the onset of jaundice. Blood and stools are infectious during the incubation period (2-6 weeks) and during early illness.
4. Clinical illness is more severe in adults than in children.
5. No carrier state, complete recovery, does not lead to chronic hepatitis.
6. Mortality is low and fulminant hepatitis is uncommon except in cases where hepatitis A occurs in a patient with chronic hepatitis C.
7. **Incubation period 2-6 weeks.**

DIAGNOSIS

Antibody to hepatitis A (anti-HAV) appears early in the course of the illness. Detection of 1gM anti- HAV is an excellent test for diagnosis of acute hepatitis A. Peak titers of 1gM occur during the first week of clinical disease and usually disappear within 3-6 months. Titers of 1gG peak after one month of the disease and may persist for years.

CLINICAL FEATURES

Pre-icteric or prodromal phase

This phase of constitutional symptoms precedes the onset of jaundice by 1-2 weeks. Onset may be abrupt or insidious.

- Initially there is flue-like illness such as malaise, easy fatigability, headache, arthralgia myalgia and upper respiratory symptoms e.g. nasal discharge, cough and pharyngitis.
- Anorexia: Out of proportion to the degree of illness.
- Nausea, vomiting are frequent, diarrhea or constipation may occur.
- Mild fever (100-102-F) with chills is usually present.
- Abdominal pain: mild and constant pain in right upper quadrant or epigastrium due to stretching of capsule of enlarged liver.
- Dark-colored urine (due to bilirubinuria) may be noticed 1-5 days prior to the onset of clinical jaundice.

Icteric phase

After 1-2 weeks patient develops jaundice. This phase is called icteric phase. With the onset of jaundice there is often improvement of the prodromal symptoms. Features of this phase are:

- Jaundice occurs in most (70-85%) adults with acute HAV infection. Jaundice is less likely in children and is uncommon in infants. The degree of icterus also increases with age.
- Liver becomes enlarged and tender with pain in right hypochondrium due to stretching of liver capsule.
- Splenomegaly and cervical lymphadenopathy are present in 10-20% of patients particularly in children.
- Dark colored urine, pale stool due to intrahepatic cholestasis.

Convalescent phase

This recovery phase comes within 3-6 weeks of illness and is characterized by increasing sense of well being, return of appetite and disappearance of jaundice, abdominal pain and tenderness.

COURSE

The acute illness subsides over 2-3 weeks with complete clinical and laboratory recovery by 9 weeks. Less than 1% develop acute fulminant hepatic failure. Relapse may occur in hepatitis A but ultimate recovery is the rule.

INVESTIGATIONS

Liver function tests (LFTs)

Bilirubin

- Bilirubin level more than 2.5 mg/dl manifests as jaundice.
- Serum bilirubin is elevated (both direct and indirect fractions increase because of hemolysis, which often occurs in acute HAV infection).
- Bilirubin level rises soon after the onset of bilirubinuria and follows rises in ALT and AST levels. Levels may be impressively high and can remain elevated for several months; persistence beyond 3 months indicates cholestatic HAV infection.
- Older individuals have higher bilirubin levels.
  - Usually bilirubin ranges from 5-20 mg/dl in icteric stage.
  - Bilirubin levels more than 20mg/dl indicate severe disease.
  - Serum bilirubin may continue to rise despite falling serum aminotransferase level.

Hepatic enzymes

- Serum aminotransferases AST, ALT are elevated often 20-fold normal. (Peak level ranges from 400-4000 IU).
- The acute level of these enzymes does not correlate with degree of liver cell damage. Level may be higher in mild disease and may not be very high in severe disease.

- After the jaundice has subsided, the AST, ALT may remain elevated for some weeks and occasionally upto 6 months.
- Serum alkaline phosphatase is elevated usually up to 3-fold normal except in case of cholestatic hepatitis.

Prothrombin time (PT) and serum albumin

Prothrombin time may be prolonged in severe hepatitis and indicates worse prognosis. Fall in serum albumin is uncommon in uncomplicated acute hepatitis.

Blood picture

WBC is normal or low, large atypical lymphocytes may be seen.

Urine analysis

- Bilirubin appears in urine (Bilirubinuria); it precedes the onset of jaundice (in prodromal stage) along with increased urinary urobilinogen.
- Mild proteinuria is common, mild microscopic hematuria may be present.
- Urobilinogen – High.

Serology for viral markers

Anti- hepatitis A antibodies (anti- HAV) IgM.

Test results for anti-HAV IgM are positive at the time of onset of symptoms and usually accompany the first rise in alanine aminotransferase (ALT) level

This test is sensitive and specific, and results remain positive for 3-6 months after the primary infection and for as long as 12 months in 25% of patients.

MANAGEMENT

Bed rest:

Bed rest is advised until clinical and laboratory evidence of acute illness has disappeared. Patient should be treated at home unless there is specific indication.

Indications for hospitalization

- Persistent vomiting
- Change in personality or sleep behavior
- Development of bruising
- Uncertain diagnosis.

Diet

High carbohydrate, high protein, low fat diet providing adequate calories (2000-3000 Kcal). Initially fruit juice, glucose, and sugarcane juice should be given to anorexic patient.

Medications

- Drugs should be avoided in severe hepatitis because they are metabolized in the liver especially sedatives and hypnotics. Paracetamol may be cautiously administered but is strictly limited to a maximum dose of 3-4 g/d in adults.

- Antiemetics for vomiting.
- Vitamins: Multivitamin supplement especially Vit. B complex and Vit. K if anorexia is marked.
- Parenteral feeding: If severe anorexia and vomiting 10% glucose by slow I/V drip 2000-2500 ml in 24 hours to prevent dehydration.
- Calamine lotion: and cholestyramine 4 mg TDS for pruritus in cholestatic jaundice.
- *Liver transplantation:* may be required for hepatic failure

PREVENTION

General measures:

- Control at the source such as hand washing by the patient after bowel movements. Proper hand washing by the medical attendant who comes in contact with contaminated utensils, bedding or clothing is essential.
- Treatment of contact with immunoglobulin and vaccination to prevent further cases of disease.
- Immunization: Long-term secondary goals include immunization, which increases herd immunity and reduces the likelihood of further outbreaks in high-risk communities.
- Public awareness: Education about transmission and prevention of transmission

Specific measures for prevention

Active immunization

Hepatitis–A vaccine (Inj. Havrix) is available. Injection is in two strengths 0.5-ml (Harvix 360 ELISA units) and 1ml strength (Harvix 720 ELISA units).

In adults more than 16 years 1ml is given initially then 1 ml after 2-5 weeks later and a booster dose of 1 ml after 6-12 months I/M into the deltoid muscle. For 1-15 years 0.5 ml according to the same schedule.

- Vaccination is recommended for patients with chronic liver disease, animal handlers, and illicit drug abusers, sewage workers and food handlers.
- Vaccine efficacy ranges from 80-100% after 1-2 doses compared to placebo.

Passive immunization

Immune globuilin should be given to unimmunized close contacts of those recently diagnosed with acute HAV infection. Dose is 0.04-0.06 ml/kg/ IM. It gives protection for 3-4 months, usually not used because it is expensive.
Passive immunization with immune globulin reduces infection when administered within 14 days of exposure (ie, postexposure prophylaxis)

COMPLICATIONS

- **Fulminant hepatic failure** in less than 1% and mortality in young adults is 0.1% that increases with age.
- **Extrahepatic complications** (rare): Acute renal failure, interstitial nephritis, pancreatitis, red blood cell aplasia, agranulocytosis, bone marrow aplasia, transient heart block, Guillain-Barré syndrome, acute arthritis, Still disease, lupuslike syndrome, and Sjögren syndrome have been reported in association with HAV infection. Autoimmune hepatitis following HAV infection may occur. These complications are all rare.
- **Cholestatic hepatitis:** Prolonged cholestasis may follow the acute infection. The frequency at which this occurs increases with age. Prolonged cholestasis is characterized by a protracted period of jaundice (>3 mo) and resolves without intervention. Ursodeoxycholic acid may shorten the period of cholestasis. The usual features of cholestatic viral hepatitis A are pruritus, fever, diarrhea, and weight loss. Serum bilirubin levels are usually greater than 10 mg/dL (conjugated hyperbilirubinemia), along with elevation of alkaline phosphatase.
  (Experience sharing: A boy of 18 years age presented with history of fever followed by jaundice that gradually decreased as evidenced by serum bilirubin reports; during recovery phase he again developed jaundice that was more intense associated with pruritus and very high alkaline phosphatase; investigations for biliary obstruction e.g ultrasound abdomen done but there was no biliary obstrction. He was assured and cholestyramine was given for pruritus, he gradually recovered.

- **Post hepatitis syndrome:** some patients may complain of fatigue, fat intolerance and right upper quadrant pain for several months after resolution of symptoms and biochemical parameters of acute hepatitis.
- **Death:** Death is rare, occurring in fewer than 0.2% of cases. Death is more frequent in elderly patients and in those with underlying liver disease.

RELAPSING HAV INFECTION

- This complication occurs in 3-20% of patients with acute HAV infection and uncommonly takes the form of multiple relapses.
- Following a typical acute course of HAV infection, a remission phase occurs, with partial or complete resolution of clinical and biochemical manifestations. The initial flare usually lasts 3-6 weeks; relapse occurs after a short period (usually <3 wk) and mimics the initially presentation, although it usually is clinically milder.
- A tendency to greater cholestasis exists in these patients. Vasculitic skin rashes and nephritis may be additional clinical clues to this syndrome.
- During relapses, shedding of virus can be detected. IgM antibody test findings are positive.
- The clinical course is toward resolution, with lengthening periods between flares. The total duration is 3-9 months.
- Corticosteroid treatment has been shown to improve the clinical course, although the course is generally benign without treatment.

Experience sharing

Liver biochemistry must be followed to establish a return to normal levels. This is not uncommon that when we ordered hepatic viral profile (identification of all other viruses such as hepatitis A, B, C, D, E) some patients were found having underlying chronic hepatitis B or C. they were diagnosed earlier and offered treatment in time. Viral profile is expensive and therefore should be advised in affording patients and in patients in whom liver biochemistry is not returning to normal.

HEPATITIS E

Hepatitis E virus is RNA virus. Hepatitis E is similar to hepatitis A in route of transmission and clinical features. It also does not transform into chronic hepatitis. It has high mortality rate (10-20%) due to fulminant hepatic failure if occurs in pregnant women.

1. Mode of transmission is water-born.
2. Clinical illness resembles hepatitis A. Hepatitis E is more severe than hepatitis A, with mortality rates in the range of 1–2%, compared with ~0.2% for hepatitis A.
3. It does not progress to chronic hepatitis.
4. Diagnosis may be confirmed with anti-HEV IgM and IgG. HEV RNA can be detected in serum or stool by PCR.
5. Prevention and control depends on good sanitation and hygiene. No vaccine is available. Immunoglobulins are also not effective in prevention of disease.
6. It has mortality from fulminant hepatic failure of 1-2%, which rises to 20% in pregnant women. Exact cause of increased mortality in pregnant women is unknown, following are the hypothesizes:
    - The enhanced sensitivity of pregnant women to endotoxin-mediated effect is well recognised and might explain the strikingly high mortality of hepatitis E in pregnancy.
    - In pregnant women, a high incidence of disseminated intravascular coagulation associated with hepatitis E

HEPATITIS B

1. **Mode of spread:**
   - Intravenous route: Transfusion of infected blood or blood products. Contaminated needles used by drug addicts, tattooists or acupuncturists.
   - Sexual intercourse with infected person because virus is present in saliva, semen and vaginal secretions.
   - From infected mother to child at the time of delivery.

2. High risk persons are IV drug abusers, patients and staff at hemodialysis centers, homosexuals, physicians, dentists, nurses and persons working in pathological laboratory and blood bank.

2. The risk of fulminant hepatitis is in 1-2% of persons with acute disease and has a case/fatality ratio of 63-93%.

3. Can lead to chronic hepatitis, carrier state or hepatocellular carcinoma.

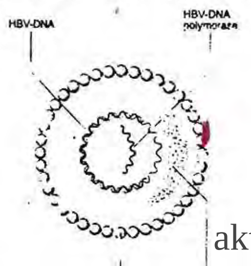
4. Perinatally infected infants generally have no clinical signs or symptoms, and infection produces typical illness in only 5-15% of children aged 1-5 years.

*6. **Incubation period: 1-6 months.***

HEPATITIS B VIRUS (HBV)

Hepatitis B virus is a DNA virus also called Dane partcle; it consists of an inner core and an outer surface capsule.

The inner core is formed of core protein (hepatitis B core antigen – HBcAg). Core protein contains DNA and DNA polymerase. The capsule protein is referred to as hepatitis B surface antigen (HBsAg). Hepatitis B virus also contains e antigen (HBeAg).



VIRAL MARKERS

The hepatitis B virus proteins act as antigens to which infected person can make antibodies. These antigens and their antibodies are important in identifying hepatitis B viral infection; these are called viral markers.

1. **Hepatitis B surface antigen (HBsAg).**
   - It is located in the capsular material of virus and is the first viral marker detectable after infection with hepatitis B.
   - It appears in the blood in late incubation period before the elevation of aminotransferases and development of clinical features of hepatitis.
   - If becomes undetectable usually after 1-2 month after the onset of jaundice and rarely persists beyond 6 months. In chronic hepatitis it remains detectable beyond 6 months.

5. **Antibodies to hepatitis B surface antigen (anti-HBs)**
   - Anti- HBs usually appear after clearance of surface antigen and persist for many years or perhaps permanently. Occasionally appearance of anti-HBs is delayed for several weeks of disappearance of surface antigen (i.e. no antigen and no antibody detectable); this is called **window period.** During this period patient is infectious, therefore negative surface antigen does not rule out infection. If doubt is there, perform anti-HBc 1gM to confirm the infection.
   - Presence of these antibodies indicates previous infection or vaccination.
   - Disappearance of HBsAg and appearance of anti-HBs indicate recovery from HBV infection.

3. **Hepatitis B core antibodies (anti-HBc)**
   - Hepatitis B core antigen (HBcAg) is located in the central part of the virus but it does not appear in the blood.
   - Anti-HBc is the first antibody to appear, it appears shortly after HBsAg is detected. 1gM type of Anti-HBc is a definitive evidence of acute infection and is predominant in first 6 months. 1gG type of anti- HBc appear during acute hepatitis and is predominant beyond 6 months and persist indefinitely, whether the patient recovers (in which anti-HBsAg is also present) or develop chronic hepatitis (in which HBsAg is also present).

4. **Hepatitis B e antigen (HBeAg).**

- HBeAg appears during incubation period shortly after detection of HBsAg. It indicates viral replication and infectivity.
- Persistence of HBeAg in serum beyond 3 months suggests in increased likelihood of chronic hepatitis - B and presence of HBeAg during chronic hepatitis B is associated with ongoing viral replication, infectivity and inflammatory liver injury.
- Disappearance of HBeAg is followed by the appearance of anti-HBe indicating diminished viral replication and decreased infectivity.
- Some rare mutant forms of virus cannot synthesize the " e" antigen **(pre-core mutant)** and PCR for HBV DNA is required to confirm viral replication. Majority of hepatitis B virus are "wild type" that synthesize " e' antigen (HBeAg)
- HBsAg- positive serum containing HBeAg is more likely to be highly infectious. For example mothers with HBsAg and HBeAg transmit hepatitis B infection to their offspring in more than 90% while mothers with HBsAg with anti- HBe rarely infect their offspring.

5. **Hepatitis B virus DNA (PCR for hepatitis B)**

The presence of hepatitis B virus DNA in serum is a more sensitive marker of viral replication and infectivity. It can be detected by polymerase chain reaction (PCR) method.

Viral markers in actue hepatitis B	
• HBsAg	• Positive
• Anti-HBc (IgM type)	• Positive
• HBeAg	• Positive
• HBVDNA	• Positive and parallels the presence of HbeAg
Viral markers in chronic hepatitis	
• HBsAg	• Positive
• Anti-HBc (IgG type)	• Positive
• Either HBeAg or anti-HBe	• May be positve
• Hepatitis B DNA	• Presence suggests continual viral replication.

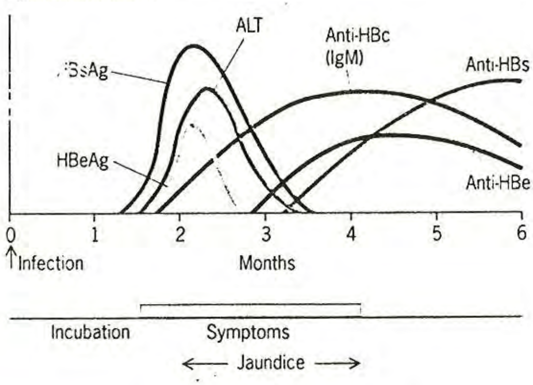
Significance of viral markers in hepatitis B

- HBsAg: present in acute or chronic infection.
- HBeAg: rises early and falls rapidly in acute hepatitis, persistence indicates development of chronic hepatitis and increased sensitivity.
- HBV DNA (PCR): implies viral replication
- Anti- HBsAg: indicates previous exposure and immunity to HBV.
- Anti- HBe: indicates diminished viral replication and low infectivity.
- Anti- HBc:
  IgM: high titer in acute and low titer in chronic infection.
  IgG: indicates past exposure to hepatitis B. Patient may be recovered or developed chronic hepatitis.

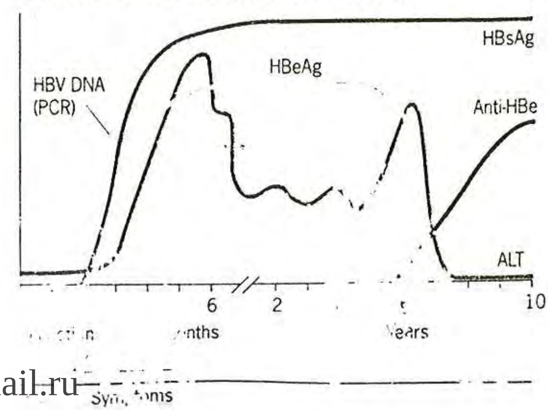
Clinical application of viral markers

- Identify hepatitis B infection (HBsAg)
- Identify either acute or chronic infection (anti-HBc antibodies)
- Identify virus replication (HbeAg) that is required for treatment with interferon .

(a) Acute infection



(b) Acute infection leading to chronic hepatitis



COMMON SEROLOGIC PATTERNS IN HEPATITIS B VIRUS INFECTION AND THEIR INTERPRETATION					
HBsAg	**Anti- HBs**	**Anti- HBc**	**HBeAg**	**Anti - HBe**	**Interpretation**
+	-	IgM	+	-	Acute hepatitis B
+	-	IgG	+	-	Chronic hepatitis B with active viral replication
+	-	IgG	-	+	Chronic hepatitis B with low replication
-	-	IgM	+ or -	-	Acute hepatitis B
-	+	IgG	-	+ or -	Recovery from hepatitis B (immunity)
-	+	-	-	-	Vaccination (immunity)
-	-	IgG	-	-	False positive or infection in remote past

Clinical significance: although it may be boring for students to remember this interpretation of viral markers yet it is very true that in clinics a number of patients come with laboratory reports and consult for expert opinion regarding their disease status and for treatment planning. This chart is very important for decision making for medical practitioners.

CLINICAL FEATURES

- Clinical features are similar to hepatitis A although the illness may be more severe; however infection maybe asymptomatic.
- In addition, a serum sickness-like immunological syndrome may be seen in acute hepatitis during prodromal stage in up to 25% of cases. This consists of rashes (e.g. urticaria, maculopapular rash, Henoch-Schonlein purpura) and polyarthritis affecting small joints.
- Fever is usually present.
  Extrahepatic immune complex- mediated conditions such as polyarteritis nodosa, or glomerulonephritis are occasionally seen

INVESTIGATIONS

Non-specific

LFTs, complete blood count, urine analysis, PT and blood sugar-as performed in hepatitis A.

Specific

- HBsAg and anti-HBc IgM should be performed. If HBsAg is positive, a full viral profile is then performed.
- In routine HBsAg is performed but it may be cleared rapidly or titer is very low, therefore anti-HBc IgM should also be performed simultaneously.
- HBV DNA (PCR) is the most sensitive test of viral replication.

COMPLICATIONS

1. Fulminant hepatic failure
2. Post hepatitis syndrome: fatigue, fat intolerance and right upper quadrant pain.
3. Chronic hepatitis
4. Cirrhosis
5. Hepatocellular carcinoma
6. Rare complications of viral hepatitis are as follows:
   - Pancreatitis, myocarditis
   - Atypical pneumonia
   - Aplastic anemia
   - Transverse myelitis
   - Peripheral neuropathy

PREVENTION OF HEPATITIS B

1. General measures:

- Careful handling of disposable needles including "no recapping" the used needles.
- Screening of donated blood for HBsAg, anti-HBc and anti-HCV.
- Unnecessary transfusions and commercially obtained blood should be avoided.
- Infected person should practice safe sex using condoms, partner should receive vaccination.
- Patient should avoid intimate contacts (e.g. sharing razors, tooth brushes) with other household members.

2. Hepatitis B vaccine

- All infants and children.
- Persons at high risk e.g.: Renal dialysis patients and attending personnel.
- Patients requiring repeated transfusions
- Spouse of HBs Ag-positive individual
- Male homosexual.
- IV drug abusers.
- New born of HBs Ag-positive mothers
- Medical staff.
- Dose: Inj. Engerix B 10µg for children aged 10 years and under while 20µg above 10 years and adults, 1/M in deltoid (not gluteal) at 0, 1, and 6 months. Soreness at the site of injection, fever, rash or flu-like illness may occur due to vaccine but uncommon.

3. Hepatitis B immune globulin (Bayhep B)

- This is recommended for individuals exposed to hepatitis B surface antigen-contaminated material via the mucus membrane or through breaks in the skin or as an accidental needle stick injury. Vaccination should be started simultaneously but at another site.
- It is also recommended for persons who have had sexual contact with patients with HBV.
- It is also indicated for newborn infant of HBsAg positive mother followed by vaccination. Passive The current recommendation for neonates of HBsAg-positive mothers is to administer HBIG 0.5 mL intramuscularly with the first dose of recombinant HBV vaccine within 12 hours of birth. In infants of infected mothers, combined treatment with the vaccine and hepatitis B immunoglobulin has 79-98% efficacy in preventing chronic HBV infection. Breast feeding is the method of choice for feeding as the breast feeding has negligible chance to transmit infection to the infant, however the infant should be vaccinated and immunoglobin should also be given to the baby. Even though the HBV antigen has been detected in breast milk, there is no evidence that breast-feeding increases the risk of mother-to-child transmission.
- Dose:0.06ml/kg IM as soon after exposure as possible (preferably within 7 days). Injection is available in 1ml (217 IU) and 0.5ml. For 60kg patient 0.06 x 60 =3.6ml
  1ml injection costs about Rs. 9000/=
  0.5ml injection costs about Rs. 5000/=

Hepatitis B surface antigen (HBsAg) carrier

Following an acute hepatitis B virus infection approximately 1-10% of patients will not clear the virus and most will become carriers of HBsAg. They are asymptomatic and have:

- HBsAg = + ve
- HBeAg = - ve
- Anti- HBe = +ve
- HBV DNA (PCR) = - ve

The carrier stage occurs more readily in with neonatal or childhood infection and in immunosuppressed patient such as with HIV infection.

They have no evidence of active liver disease and are not highly infective.

Most of them do not develop active liver disease but the risk of hepatocellular carcinoma becomes increased.

There are also asymptomatic people who have HBeAg, and HBV DNA in their serum. They may have normal LFTs for many year; disease develops when immune balance changes and lymphocytes recognize infected hepatocytes causing hepatitis. These patients need follow up.

SEQUELAE OF HEPATITIS B

The majority of patients recover completely from acute hepatitis B, about 1% develop fulminant hepatic failure. About 1-10% of immunocompetent adult patients develop chronic hepatitis B virus infection in which 10-30% develop chronic hepatitis, cirrhosis and hepatocellular carcinoma while 70-90% become asymptomatic carrier of HBsAg and develop hepatitis later in life when immune system recognizes infected hepatocytes. Chronicity develops in as many as 90% of infected neonates and infants.

HEPATITIS C

- Hepatitis C virus (HCV) is a RNA virus
- Mode of transmission: Blood and blood products, IV drug abuse, sexual contact (low risk), vertical transmission from infected mother to child, transmission via breast feeding has not been documented.
- HCV caused 90% of post-transfusion hepatitis before serological tests that allowed the screening of blood donors. Intravenous drug abusers are at high risk of HCV infection.
- Incubation period averages 6-7 weeks.
- More than 85% of cases lead to chronic hepatitis. Cirrhosis develops in 20-30% within 5-30 years and about 15% develop hepatocellular carcinoma. Male patients and people acquiring infection over 40 years have more rapid development of fibrosis.
- Hepatitis C may be a pathogenic factor in glomerulonephritis, autoimmune thyroiditis, idiopathic pulmonary fibrosis and probably lymphoma.

Clinical features

In acute hepatitis C clinical illness is often mild, usually asymptomatic with about 10% of patients have mild, flu-like illness and a rise in serum aminotransferases. Most of the patients are diagnosed years later with complications of chronic liver disease.

Diagnosis

Diagnosis of hepatitis C is frequently by exclusion with negative markers for hepatitis A and hepatitis B. HVC RNA (PCR) is positive 1-2 weeks after infection. Anti-HCV antibodies in serum take 6 weeks to develop.

Treatment

Alpha interferon for 6-24 weeks in acute hepatitis decreases risk of chronic hepatitis.

HEPATITIS D

1. Hepatitis D virus (HDV) is a RNA virus.
2. It requires hepatitis B virus for replication and has the same sources and mode of spread as HBV especially IV drug abuse.
3. Infection may be simultaneous with HBV or as superinfection in chronic carriers of hepatitis B- virus.
4. It causes chronic hepatitis and cirrhosis in 60-70% of cases.
5. Fulminant hepatitis is more common with simultaneous infection
6. Diagnosis: serum 1gM anti-bodies at the same time as 1gG HBc.
7. Treatment: Alpha interferon produces remission but relapse is common.

HEPATITIS G

1. Hepatitis G virus is transmitted through skin and causes mild hepatitis.
2. Mostly affected persons are IV drug abusers and hemodialysis patients.
3. It can lead to chronic hepatitis.
4. Diagnostic tests are not yet available.

NON-A-E HEPATITIS

In about 10-15% of cases of acute viral hepatitis type of virus is not identified they are termed as non –A-E hepatitis.

Clinical and Epidemiologic Features of Viral Hepatitis

Feature	HAV	HBV	HCV	HDV	HEV
Incubation (days)	15–45, mean 30	30–180, mean 60–90	15–160, mean 50	30–180, mean 60–90	14–60, mean 40
Onset	Acute	Insidious or acute	Insidious	Insidious or acute	Acute
Age preference	Children, young adults	Young adults (sexual and percutaneous), babies, toddlers	Any age, but more common in adults	Any age (similar to HBV)	Young adults (20–40 years)
Transmission:					
Fecal-oral	+ + +	–	–	–	+ + +
Percutaneous	Unusual	+ + +	+ + +	+ + +	–
Perinatal	–	+ + +	±[a]	+	–
Sexual	±	+ +	±[a]	+ +	–
Clinical:					
Severity	Mild	Occasionally severe	Moderate	Occasionally severe	Mild
Fulminant	0.1%	0.1–1%	0.1%	5–20%[b]	1–2%[c]
Progression to chronicity	None	Occasional (1–10%) (90% of neonates)	Common (50–70% chronic hepatitis; 80–90% chronic infection)	Common[d]	None
Carrier	None	0.1–30%[e]	0.5–1.0%	Variable[f]	None
Cancer	None	+ (neonatal infection)	+	±	None
Prognosis	Excellent	Worse with age, debility	Moderate	Acute, good Chronic, poor	Good
Prophylaxis	IG Inactivated vaccine	HBIG Recombinant vaccine	None	HBV vaccine (none for HBV carriers)	Unknown
Therapy	None	Interferon 40% effective	Interferon 50% response; sustained response <15%	Unknown	None

FULMINANT HEPATIC FAILURE (FHF)

Fulminant hepatic failure may be defined as severe hepatic failure with development of hepatic encephalopathy within 8 weeks after the onset of acute liver disease due to any cause, in the absence of evidence of pre-existing liver disease, to distinguish it from deterioration in chronic liver disease that also leads to hepatic enceohalopathy.

Subfulminant hepatic failure is the term used when encephalopathy occurs between 8 weeks and 6 months after the onset of acute liver disease and carries an equally poor prognosis.

About 70% cases are caused by acute viral hepatitis (50% due to hepatitis B) other causes are hepatitis A, E, D).

Hepatitis A superimposed on chronic hepatitis C is associated with high risk of fulminant hepatic failure. Other causes are drugs, shock, malignancy (most commonly lymphomas), Wilson's disease and fatty liver of pregnancy. Liver transplantation is the treatment.

Clinical Features

- Jaundice
- Hepatic encephalopathy (details are given in the complications of cirrhosis)
- Small liver on examination

Investigations

1. Aminotransferases ALT, AST are high initially but with progressive liver damage they become low, therefore their level do not correlate the liver injury.
2. Prothrombin time (PT) becomes prolonged as the liver is unable to synthesize coagulation factors. Percutaneous liver biopsy is therefore contraindicated.
3. EEG: may be helpful in grading the encephalopathy.

Investigations to determine the cause of FHF

- Toxicology screen of blood and urine (to identify toxin if present)
- IgM anti-HBs.
- IgM anti-HAV
- Antibodies against HEV, cytomegalovirus (CMV), herpes simplex, Epstein-Barr virus (EBV)
- Serum ceruloplasmin, serum copper, urinary copper (for Wilson disease)
- Autoantibodies: ANF, AMA, ASMA, LKM (for autoimmune hepatitis)
- Ultrasound of liver and Doppler of hepatic veins
- Chest radiograph

Poor prognostic factors in FHF
Indicating a need for liver transplantation

Non- Paracetamol (3 of following 5 factors)
- Drug or non-A-E hepatitis
- Age <10 or > 40 years
- Interval from onset of jaundice to encephalopathy > 7 days
- Serum bilirubin > 18mg/dl
- PT > 50 sec

Paracetamol
- Arterial pH < 7.3

OR
- Serum creatinine > 300μmol/L
- PT > 100
- Grade III- IV encephalopathy

Clinical grading of hepatic encephalopathy

Clinical grade	Clinical signs
Grade 1	Poor concentration, slurred speech, slow mentation, disordered sleep rhythm
Grade 2	Drowsy but easily arousable, occasional aggressive behavior
Grade 3	Marked confusion, drowsy, sleepy but responds to pain and voice.
Grade 4	Unresponsive to voice, may or may not respond to painful stimuli, unconscious

MANAGEMENT

There is no specific treatment. Supportive therapy for the following conditions is necessary:

1. **Hepatic encephalopathy**
   Encephalopathy occurs due to nitrogenous substances (e.g. ammonia) in portal circulation which by-pass the liver (because liver becomes unable to detoxify them) & produce cerebral dysfunction.

Therefore following measures should be done to reduce ammonia production:
- Protein intake should be restricted (to prevent nitrogenous substance formation)
- Syp. Metronidazole (Flagyl) 200 mg 4-times daily.
- Lectulose (Duphalac) 30 ml 6 hourly to empty the bowel (which contains nitrogenous substances).

2. **Cerebral edema**

It is the major cause of death. When signs of raised intracranial pressure are present 20% mannitol (1 gm/Kg body weight) should be infused I/V, this may need to be repeated. There is no role of steroids.

3. **Nutrition**
- Glucose (300g/d) orally or by nasogastric tube or I/V 10% dextrose (because glycogen synthesis by the liver is impaired).
- Blooc glucose level should be checked 2 hourly because potentially fatal hypoglycemia often occurs.
- Potassium and calcium should be corrected if there is hypokalemia and hypocalcemia.

4. **Cardiovascular functions**
- I/V infusion of fluid, colloid & blood
- Regular recording of pulse, B.P. & urine output.

5. **Hemorrhage**
- Impaired homeostasis due to failure of coagulation factor production can result in bleeding from any site especially from GIT. Coagulopathy is managed with intravenous vitamin K, platelets, blood or fresh frozen plasma (FFP). H2-blocker e.g. ranitidine (Inj. Zantac 50mg) I/V 12 hourly should be given to prevent GIT bleeding.

6. Infection

- If there is infection, broad spectrum antibiotics should be given I/V/

7. Renal failure

- Dailysis; if there is renal failure

8. Acetylcysteine

- Acetylcysteine (antidote of paracetamol poisoning) is also effective to improve cerebral blood flow in all patients with FHF due to any cause.

9. Liver transplantation

Liver transplantation is the major advance for patients with fulminant hepatic failure. Emergency transplantation should be considered for patients with stage II to stage III encephalopathy and survival rate is 80% at one year. Compared with chronic hepatitis B, liver transplantation for fulminant hepatitis B is less likely to result in reinfection of the graft with hepatitis B virus.

Complications of fulminant hepatic failure

1. Encephalopathy
2. Cerebral edema
3. Respiratory failure
4. Hypotension
5. Hypothermia
6. Infection
7. Bleeding
8. Pancreatitis
9. Renal failure
10. Metabolic
    - Hypoglycemia
    - Hypokalemia
    - Hypocalcemia
    - Hypomagnesemia
    - Acid – base balance

CHRONIC HEPATITIS

Hepatitis lasting 6 months or longer is known as chronic hepatitis. It is demonstrated by persistently abnormal serum aminotransferase levels and characteristic histologic findings.

Chronic hepatitis B and C are spreading very rapidly in Pakistan. Patients visit to consultants with their reports and ask whether they should receive treatment or not. Therefore it is obvious to learn management of chronic hepatitis accurately.

CLASSIFICATION

- Chronic hepatitis is best classified according to the etiology, grade of inflammation and stage of fibrosis. Terms such as chronic persistent and chronic active hepatitis are no longer used.

Classification by etiology

- Due to viral disease (most common cause)
- Due to autoimmune disease
- Drug-induced
- Unknown cause.

CAUSES OF CHRONIC HEPATITIS	
Viral Hepatitis B + delta virus Hepatitis C **Autoimmune** **Drugs** Methyldopa, isoniazid, ketoconazole, nitrofurantoin)	**Hereditary** Alpha – 1 antitrypsin deficiency Wilson's disease **Others** Ulcerative colitis Alcohol

Classification by grade

Grade is the histological assessment of inflammatory activity (determined by the numbers and location of inflammatory cells and is based upon examination of liver biopsy. The important histological feature is the degree of periportal, portal and lobular inflammation including piecemeal necrosis. The most popular scoring system for grading of inflammatory process is Histologic Activity Index (HAI) developed by Knodell and Ishak. Based on

degree of inflammation chronic hepatitis can be graded as mild, moderate or severe.

Classification by stage

The stage of chronic hepatitis, which reflects the level of progression of the disease, is based on the degree of fibrosis. Staging is based on degree of fibrosis as follows:

0 = no fibrosis
1 = mild fibrosis
2 = moderate fibrosis
3 = severe fibrosis
4 = cirrhosis

CHRONIC HEPATITIS B

Chronicity after acute hepatitis depends on age of the patient; 90% in newborn who get infected at birth while only 1% in immunocompetent young adults. However most of the chronic hepatitis B among adults develops without history of acute hepatitis.

- Management strategy of chronic hepatitis is discussed in detail especially for practioners, students should know the issues related to management, however they may ignore the details of guidelines.

In the management of chronic hepatitis B, two factors are very important 1) presence or absence of HBeAg, (2) serum ALT/ AST elevated equal to or more than 2 times normal or these enzymes are normal or slightly elevated..

Chronic hepatitis B can be separated into two forms based on the presence of the hepatitis B e antigen (HBeAg) and antibody (anti-HBe).

1. **HBeAg-positive** chronic hepatitis B occurs during the early phases of chronic HBV infection and is characterized by extremely high HBV replication and persistently or intermittently increased aminotransferase levels. Majority of such patients, if left untreated, maintain high HBV replication and severe liver necroinflammation, which is associated with worsening fibrosis, the development of cirrhosis and an increased risk of hepatocellular carcinoma.
2. **HBeAg-negative** chronic hepatitis B, also referred to as anti-HBe-positive chronic hepatitis B, represents a rather late phase in the course of chronic HBV infection. HBeAg-negative chronic hepatitis B represents a potentially severe and progressive form of chronic liver disease with very rare spontaneous remissions, frequent progression to cirrhosis and increased risk of the development of hepatocellular carcinoma.

If serum ALT/ AST are normal (or not elevated to twice normal) usually treatment is not advised.

There are two factors important for prognosis point of view:- one is histology (grading and staging) and other is hepatitis B virus replication (viral load) demonstrated by presence of HBeAg and HBV DNA (PCR).

CLINICAL FEATURES

- Mostly patients are asymptomatic, diagnosed when screened for blood donation or when complications develop.
- Patient may present with fatigue and persistent or intermittent jaundice.

INVESTIGATIONS

- Serum aminotransferaes ALT and AST are modestly raised in the range of 100-1000 units. ALT is higher than AST in chronic hepatitis as in acute hepatitis but AST becomes higher when cirrhosis is established.
- Serum alkaline phophatase is marginally elevated or normal.
- Serum bilirubin may be elevated but often normal.
- Prolonged PT and hypoalbuminemia occur in severe or end-stage cases.
- HBsAg and HBV DNA are found in the serum, usually with HBeAg.
- Biopsy ranges from near normal to a full-blown cirrhosis.

Investigations in chronic hepatitis B

LFTs

- Bilirubin usually normal
- Liver enzymes ALT, AST raised
- Alkaline phosphatase slightly elevated or normal

PT: normal until severe or end stage disease.

Viral markers

HBsAg, HBV DNA (PCR) are found in serum, usually with HBeAg.

Liver biopsy: near normal to full- blown cirrhosis.

Current Management Recommendations for Patients with Chronic Hepatitis B

Type of CHB	HBeAg	anti-HBe	ALT/AST	Serum HBV-DNA*	Liver histology	Management
HBeAg-positive CHB	+	-	< 2 × ULN	High	No need for liver biopsy	Monitor ALT/AST every 3 months
	+	-	>/= 2 × ULN	High	Moderate/severe CHB†	Therapeutic intervention
Inactive chronic HBV carrier	-	-/+	< ULN	Low	No need for liver biopsy	Monitor ALT/AST every 6 months
HBeAg-negative CHB	-	-/+	> ULN	High or low	Moderate/severe CHB†	Therapeutic intervention
	-	-/+	> ULN	High or low	Minimal/mild CHB	Monitor ALT/AST every 3-6 months

ALT= alanine aminotransferase; anti-Hbe= hepatitis B e antibody;
AST= aspartate aminotransferase; CHB,=chronic hepatitis B; HBeAg=hepatitis B e antigen;
HBV=hepatitis B virus; ULN= upper limit of normal.
* High and low serum HBV-DNA levels are currently considered as >/= and < 10^5 copies/mL.[12,14]
† Moderate/severe CHB: liver biopsy with at least moderate necroinflammatory activity (grading) and/or moderate fibrosis (staging).

Treatment strategy according to ALT level

ALT elevated

HBeAg positive
Start treatment with interferon, lamivudine or adefovir.

HBeAg negative
- HBV DNA (PCR) positive = start treatment with adefovir, lamividine or interferon.
- HBV DNA (PCR) negative = look for other causes and repeat DNA.

ALT normal (low efficacy with current treatment)
HBeAg positive → wait for 6 months
- ALT becomes elevated = start treatment
- ALT remains normal→ liver biopsy→ Histologic activity index (HAI) < 3 = no treatment
  Histologic activity index (HAI) > 3 = start treatment
- ALT normal, PCR for HBV positive (along with anti- HBe antibodies) perform liver biopsy→ Histologic activity index (HAI) < 3 = no treatment
  Histologic activity index (HAI) > 3 = start treatment

American Association for the Study of Liver Diseases (AASLD) guidelines for the management of chronic hepatitis B

	HBeAg	HBV DNA	ALT	Management plan
1	+	+	≤ 2 times normal	Low efficacy with current treatment
2	+	+	> 2 times normal plus moderate to severe hepatitis on biopsy	Start therapy with interferon alfa, lamividine or adefovir *Duration of treatment* • Interferon: 16 weeks • Lamividine : minimum 1 year • Adefovir : minimum 1 year
3	-	+	> 2 times normal	Interferon,, lamividine or adefovir may be used *Duration* • Interferon: 1 year • Lamividine: more than 1 year • Adefovir: more than 1 year
4	-	-	<2 times normal	No treatment required
5	±	+	Cirrhosis	Compensated: lamividine or adenofir Decompensated: lamividine or adenofir
6	±	-	Cirrhosis	Compensated: observe Decompensated: liver transplantation

TREATMENT

Three drugs are approved for treatment of chronic hepatitis B:

- Interferon: interferon alfa, peginterferon alfa-2b
- Nucleoside analogues: lamivudine and adefovir.

Treatment may be initiated with any of the above agents, however each drug has some advantages and some limitations.

Interferon Therapy

Suitable candidates for interferon have:

- Chronic hepatitis on liver biopsy
- Elevated aminotransferases
- Detectable markers of chronic replicative hepatitis B such as HBeAg, and HBV DNA,
- Compensated liver disease (not developed cirrhosis).
- Immunocompetent patient (not in HIV).
- Acquision of HBV infection in adulthood (not in infants)

PREDICTORS OF NONRESPONSE TO INTERFERON THERAPY

- Childhood infection
- Low serum ALT (less than 2 times normal)
- High serum hepatitis B virus DNA levels
- Disease caused by precore mutant (HBeAg negative)
- Mild grade of inflammation on liver biopsy
- Coexisting hepatitis D virus infection
- Immunosuppression such as HIV
- Male sex
- Asian ethnicity

Patients not suitable for interferon therapy

- Asymptomatic patients
- Normal aminotransferases (ALT, AST)
- Non-replicative hepatitis B carriers having no HBeAg (pre- core mutant) and HBV DNA.
- Decompensated liver disease (i.e. cirrhosis). Interferon therapy in cirrhosis may lead to hepatic failure.

Response to interferon therapy

- About 25 - 40% of treated patients will respond with normalization of aminotransferase levels, disappearance of HBeAg and HBV DNA, appearance of anti- HBe, and improved survival.
- Response is most likely in patients with viral load (HBV DNA) level less than 200 pg/ml and high aminotransferase levels (more than 100-200 units).Relapses are uncommon in such complete responders.

Dosage and duration of interferon

- Interferon alfa-2b (Inj. Uniferon) 5 million units daily or 10 million units 3-times per week subcutaneously for 4 months. (Cost 5MU = about Rs.1500).
- Peginterferon alfa- 2b 100μg once a week subcutaneously for 4 months. Peginterferon is superior to interferon-alfa-2b in response but it is expensive.

Side effects

- Flu-like symptoms such as fever, malaise, headache, myalgia, anorexia, nausea, vomiting, and diarrhea.
- Alopecia, depression, and bone marrow suppression (neutropenia, thrombocytopenia).
- Depression, neuropathy
- Hypothyroidism

Contraindications

Contraindications of interferon are cirrhosis, cytopenias, psychiatric disease, and autoimmune disease.

2. LAMIVUDINE

- Lamivudine (Tab. Zeffix 100mg) is the anti- HBV nucleoside analogue given one tablet daily for indefinite time (usually more than 1 year).
- It reliably suppresses HBV DNA in serum, improves liver histology in 40% of cases, and leads to normal ALT levels and HBeAg in 20% of cases after one year therapy.
- This drug can be used even in patients with cirrhosis. However hepatitis activity may recur when the drug is stopped and long-term use of drug leads to emergence of lamivudine resistant strain of virus.
- It can also be given in HBeAg negative chronic hepatitis B (pre- core mutant).
- Combination of interferon and lamivudine proved no additional benefit over single therapy.
- Long term use leads to development of drug-resistant hepatitis B virus mutant (in long term use adefovir is preferred because it is associated with a low incidence of resistance).
- Side-effects are headache, insomnia, fatigue, stomach aches, diarrhea and chills.
- Cost: 1tab = about Rs.120

ADEFOVIR DIPIVOXIL.

Adefovir, a nucleotide analogue of adenosine, is a new anti-HBV agent that is administered orally as adefovir dipivoxil. Dose is 10 mg daily for chronic hepatitis B, which can be safely administered. Side effects from adefovir include general weakness, headache, abdominal pain, nausea, flatulence, diarrhea and dyspepsia.

THREE TREATMENT OPTIONS FOR CHRONIC HEPATITIS B

	Advantages	Disadvantages
Interferon	• Short duration of treatment. • More sustained response. • Lack of resistant mutant	• More side effects • Expensive • Not used in cirrhosis. • Not effective in HbeAg –ve
Lamividine	• Oral administratio n • Less side effects, better tolerated. • May be used in cirrhosis. • May be used in HbeAg -ve	• Sustained response in mionority after withdrawal of therapy, therefore requires indefinite therapy. • Emergence of resistant hepatitis B virus mutant
Adefovir	• Oral administratio n • Less side effects, better tolerated • Low incidence of emergence of resistant hepatitis B virus mutant • May be used in cirrhosis. • May be used in HbeAg – ve	• Sustained response in mionority after withdrawal of therapy, therefore requires indefinite therapy.

RE –TREATMENT

Patients with chronic hepatitis B, who fail to achieve a sustained response after a first course of IFN-α, can be re-treated with a second course of IFN-α, lamivudine or adefovir dipivoxil. In particular, re-treatment with IFN-α has been found to have a similar efficacy to that of an initial course of IFN-α in patients with HBeAg-positive and HBeAg-negative chronic hepatitis B. Therefore, re-treatment with IFN-α can be recommended in chronic hepatitis B patients who fail a first course of IFN-α. In clinical practice, however, many patients are unwilling to be re-treated with IFN-α due to their experience of the efficacy and impact on the quality of life of the first course. This may be improved in the future with the use of pegylated forms of IFN-α. The efficacy of lamivudine or adefovir dipivoxil monotherapy is similar in both treatment-naive and previously IFN-α-treated patients with chronic hepatitis B, as shown in several trials.

Patients who do not initially respond to lamivudine may be treated with IFN-α or adefovir dipivoxil or referred for treatment within clinical trials with other anti-viral agents

CHRONIC HEPATITIS C

Patients with chronic hepatitis C are usually asymptomatic being discovered only following a routine biochemical test when elevations in the aminotransferases (usually ALT) are noticed. The elevation of ALT may be minimal or fluctuating, and about 25% of cases have normal ALT. These patients are diagnosed when anti- HCV is detected on blood donation. However severe chronic hepatitis and even cirrhosis can be present with only minimal elevation of aminotransferases. Progression to cirrhosis occurs in 20% of affected patients in 20 years with an increased risk in men, alcoholics,immunosuppresed and who acquire HCV infection after age 40.

Genotypes of hepatitis C virus

- There are 11 different Genotypes to Hepatitis C and at least 50 different Sub-types. The Genotype is now used, in conjunction with a liver biopsy, to help determine if treatment is necessary and is used in deciding how long the treatment regime should be. Genotype 1 is the most difficult to treat, therefore if the patient has this genotype he should be on treatment for 48 weeks. Any other genotype should be treated for 24 weeks. Patients with genotypes 2 and 3 are two to three times more likely to respond to interferon-based therapy than patients with genotype 1.

- The term *genotype* refers to genetic heterogeneity amongst HCV isolates worldwide, and reflects the accumulation of mutations during the long-term evolution of these viruses
- Genotype 3 is common in Pakistan
- Genotypes 1a, 1b, 2a, 2b, 2c, and 3a account for more than 90% of the HCV infections in North and South America, Europe, Russia, China, Japan, Australia, and New Zealand. Genotype 3a is more common among younger populations. Other subtypes of genotype 3 are highly prevalent in Nepal, Bangladesh, India, and Pakistan. Most infections in Egypt are genotype 4a, and this and other subtypes of genotype 4 are found in Central Africa. Genotype 5a accounts for about 50% of infections in South Africa. Genotypes 4 and 5 are found only sporadically outside Africa. Genotype 6 isolates are primarily found in Southeast Asia.

INVESTIGATIONS

Anti- HCV antibodies

Diagnosis is made by finding anti-HCV antibody in the serum, however it only indicates exposure to hepatitis C.

PCR for HCV

To confirm that the viremia is present HCV RNA should be performed by PCR method, that measures qualitative and quantitative HCV RNA (Viral load).

LFTs

Liver function tests are required to see aminotransferases (ALT/AST). ALT levels, particularly if tested over an extended period, are reasonably accurate reflections of disease activity. Thus, patients with repeatedly normal ALT levels usually have mild necroinflammatory activity on liver biopsy. Furthermore, patients who maintain ALT levels above 5 times the upper limit of normal usually have marked necroinflammatory activity. But for the majority of patients with mild-to-moderate ALT elevations, the actual level is not very predictive of liver biopsy findings.

Normal Serum ALT Levels

Some patients with chronic hepatitis C have normal serum alanine aminotransferase (ALT) levels, even when tested on multiple occasions. In this and other situations in which the diagnosis of chronic hepatitis C may be questioned, the diagnosis should be confirmed by testing for HCV RNA. The presence of HCV RNA indicates that the patient has ongoing viral infection despite normal ALT levels.

In individuals with normal aminotransferase values and extensive hepatic fibrosis (bridging fibrosis or cirrhosis), treatment should be considered, and liver biopsy is the only available method to obtain the necessary information to guide this decision. In individuals with normal aminotransferase values and extensive hepatic fibrosis (bridging fibrosis or cirrhosis), treatment should be considered, and liver biopsy is the only available method to obtain the necessary information to guide this decision.

HCV genotyping

HCV genotyping should also be performed because genotype 2 and 3 have good response to interferon while genotype 1 and 4 have poor response.

Liver biopsy

Liver biopsy is optional in the management of chronic hepatitis C, some advocate and some are against it. Liver biopsy becomes very valuable when there is confusion either to start therapy or not such as in case of normal ALT, here initiation of therapy depends on biopsy findings.

A liver biopsy provides much information. It provides confirmation of the diagnosis, exclusion of other liver diseases, and assessment of the grade and stage of the disease. Liver biopsy is performed if active treatment is being considered, to assess the severity and degree of liver damage and to assess the need for treatment because ALT may be fluctuating or normal.

Regardless of the level of ALT, a liver biopsy should be done when the results will influence whether treatment is recommended, but a biopsy is not mandatory in order to initiate therapy.

TREATMENT

Who Should Be Treated?

Treatment is appropriate for patients with chronic hepatitis C with following factors:

- Elevated serum ALT(>1.5 times normal).
- Chronic hepatitis of moderate severity on liver biopsy (treatment of histologically mild hepatitis with interferon is controversial)
- Detectable HCV RNA (positive PCR)
- The presence of compensated cirrhosis is not a contraindication.

Who Should Not Be Treated?

Therapy is inadvisable outside of controlled trials for patients who have

- Clinically decompensated cirrhosis because of hepatitis C
- Normal aminotransferase levels (perform biopsy, if hepatitis is moderate then start treatment)
- A kidney, liver, heart, or other solid-organ transplant
- Specific contraindications to either monotherapy or combination therapy

Treatment of Persons with Normal Serum Aminotransferase-Values

Management of persons with normal serum aminotransferase values is important since up to 60% of HCV-infected first-time blood donors and injection drug users have been reported to have normal-values.

Nonetheless, for purposes of this discussion, a person is considered to have normal ALT levels when there have been two or more determinations identified to be in the normal range of a licensed laboratory over six or more months.

Currently, there is disagreement in regard to whether HCV-infected persons with established normal ALT values warrant treatment. On the one hand, individuals with persistently normal ALT values generally have less severe liver disease than that observed in those with abnormal aminotransferase values. Thus, some believe that liver disease progression is uncommon in most such individuals and the adverse events associated with current therapy outweigh the probability that existing treatmentwill be successful. On the other hand, biopsies of those with normal aminotransferase values have revealed bridging fibrosis or cirrhosis in 1% to 10% of cases, and at least portal fibrosis in a greater proportion. Even though the majority of HCV-infected persons with minimal fibrosis rarely develop progressive disease, histological and clinically advancing liver disease has clearly been documented despite persistently normal aminotransferase values. In addition,the response rate in this group to interferon alfa and ribavirin appears to be similar to that of individuals with abnormal values.

Recommendation

Regardless of the serum aminotransferase levels, the decision to initiate therapy with interferon and ribavirin should be individualized based on the severity of liver disease by liver biopsy, the potential of serious side effects, the likelihood of response, and the presence of co-morbid conditions.

ANTIVIRAL THERAPY

Interferon plus ribaverin combination therapy

Interferon

- Interferon alpha-2b (Inj. Uniferon) or Interferon alpha-2a (Roferon – A) 3 million units 3-times per week and ribavirin 10.6mg/kg/daily in two divided doses. Pegylated interferon is now preferred to interferon alfa. Duration of treatment 6 months if genotype 2 or 3 and 12 months for genotype 1 and 4 is recommended. Fortunately in Pakistan most of HBV is genotype 3 and chances of response to interferon are high.
- Combination of interferon and ribavirin results in higher sustained response.
- About 85-90% response occurs within first three months; response thereafter is rare.
- The effect of treatment is monitored by measurement of the aminotransferases and HCV RNA at 3 months. If the aminotransferases remain abnormal and HCV RNA is present in the serum at three months treatment is stopped because a response to further treatment is then unlikely.

- After 6 months of therapy, 40-50% of patients respond with normal aminotransferaes and about half of these will relapse after treatment while 15-25% sustain response.
- Patients older than 60 years also should be managed on an individual basis, since the benefit of treatment in these patients has not been well documented and side effects appear to be worse in older patients. However, even patients in their late seventies have been successfully treated for hepatitis C.

Interferon preparations

There are several forms of alpha interferon such as alfa-2a, alfa-2b, consensus interferon. These are standard forms of interferon, however, are now being replaced by pegylated interferons (peginterferons).

Peginterferon is alfa interferon that has been modified chemically by the addition of a large inert molecule of polyethylene glycol. Pegylation changes the uptake, distribution, and excretion of interferon, prolonging its half-life.

Peginterferon can be given once weekly and provides a constant level of interferon in the blood, whereas standard interferon must be given several times weekly and provides intermittent and fluctuating levels.

In addition, peginterferon is more active than standard interferon in inhibiting HCV and yields higher sustained response rates with similar side effects. Because of its ease of administration and better efficacy, peginterferon has been replacing standard interferon.

Standard interferon

- **Alpha 2a:** (Roferon – A) 3 million units 3-times per week
- **Alpha 2b:** (Uniferon) 3 million units 3-times per week
- **Consensus interferon** : 9mg 3-times per week

Pegylated interferon (peginterferon)

Two forms of peginterferon have been developed such as:

- Peginterferon alfa-2a (Pegasys)
- Peginterferon alfa-2b (Pegintron)

These two products are roughly equivalent in efficacy and safety, but have different dosing regimens.

Peginterferon alfa-2a is given subcutaneously in a fixed dose of 180 micrograms (mcg) per week.

Peginterferon alfa-2b is given subcutaneously weekly in a weight-based dose of 1.5 mcg per kilogram per week (thus in the range of 75 to 150 mcg per week).

Side effects of interferon

- Flu-like symptoms such as fever, malaise, headache, myalgia, anorexia, nausea, vomiting, and diarrhea.
- Alopecia, depression, and bone marrow suppression (neutropenia, thrombocytopenia). Therefore blood count should be checked at week 1, 2, and 4, and monthly afterward.
- Depression, neuropathy
- Hypothyroidism
- Contraindications of interferon are cirrhosis, cytopenias, psychiatric disease, and autoimmune disease.

Ribavirin

Ribavirin (Ribazole cap. 100, 200,400mg, tab. 500, 600mg) a nucleoside analog twice daily along with interferon results in higher sustained response rate.

Side effects

- Hemolysis. Ribavirin should also be avoided in persons over age 65 because in whom hemolysis may pose risk of angina and stroke.
- Teratogenicity: It is teratogenic and women taking ribavirin should practice strict contraception (if man taking the drug, he must be avoiding impregnating the women) until 6 months after completion of therapy.

Strategy for treatment of hepatitis C

Factor	*Group I*	*Group II*	*Group III*	*Group IV*
Anti- HCV	+	+	+	-
HCV RNA (PCR)	-	+	+	+
ALT	N	N	raised	N
Management	No	Follow up	Interferon + ribavirin	Liver biopsy

AUTOIMMUNE HEPATITIS

Autoimmune hepatitis is a chronic disorder characterized by continuing hepatocellular necrosis with fibrosis leading to cirrhosis and hepatic failure as a result of autoimmune process against liver antigen.
There is association with other autoimmune diseases e.g. pernicious anemia, thyroiditis and Coomb's positive hemolytic anemia.

Favorite question in D/D of chronic liver disease in postgraduate exams.

CLINICAL FEATURES

- The onset of disease may be insidious or abrupt, like acute hepatitis (in 40%).
- Women are affected more often than men (70-80% of patients are women).
- Autoimmune hepatitis usually is detected in the third to fifth decades of life, but young children and older adults also are affected.
- Autoimmune hepatitis may present as acute hepatitis, chronic hepatitis, or well-established cirrhosis. Approximately one third of patients present with symptoms of acute hepatitis marked by fever, hepatic tenderness, and jaundice. In some patients, the acute illness may appear to resolve spontaneously; however, patients invariably develop signs and symptoms of chronic liver disease. Other patients experience rapid progression of the disease to acute liver failure, as marked by coagulopathy and jaundice. Ascites and hepatic encephalopathy also may ensue.
- There are two peaks in presentation. In the peri- or postmenopausal woman, patient may be asymptomatic or with fatigue and the disease being discovered by abnormalities in liver biochemistry or because of signs of chronic liver disease on routine examination.
- In the teenage and early twenties, disease often presents as acute hepatitis or repeated bouts of acute hepatitis with jaundice and very high aminotranferases. This age group often has features of cirrhosis with hepatosplenomegaly, cutaneous striae, acne, amenorrhea, hirsutism and sometimes ascites.
- Features of autoimmune disease may be present such as fever, migratory polyarthritis, glomerulonephritis, thyroiditis, pleurisy, pulmonary infiltration, Sjogren's syndrome and primary sclerosing cholangitis.

On examination patient may present with

- Signs of chronic liver disease
- Hepatosplenomegaly
- Sometimes Cushingoid face with acne and hirsuities may be present.
- Jaundice may be present.

SYMPTOMS OF CHRONIC AUTOIMMUNE HEPATITIS

- Fatigue
- Upper abdominal discomfort
- Mild pruritus
- Anorexia
- Myalgia
- Diarrhea
- Cushingoid features
- Arthralgias
- Skin rashes (including acne)
- Edema
- Hirsutism
- Amenorrhea
- Chest pain from pleuritis
- Weight loss and intense pruritus (unusual)

COMMON FINDINGS ON PHYSICAL EXAMINATION

- Hepatomegaly (83%)
- Jaundice (69%)
- Splenomegaly (32%)
- Spider angiomata (58%)
- Ascites (20%)
- Encephalopathy (14%)

INVESTIGATIONS

1. Serum ANA, ASMA, anti- LKM serum protein electrophoresis (SPEP) and urgent liver biopsy.
2. Other tests
   - Aminotransferases are raised, with lesser elevations in alkaline phosphatase and bilirubin
   - **Serum gamma globulin** – raised, frequently twice normal (up to 5-6 g/dl). There is marked increase in IgG.
   - Prothrombin time – raised
   - Plasma albumin – low
   - Bilirubin – raised but usually not more than 6mg/dl.
   - Normocytic normochromic anemia with thrombocytopenia and leukopenia is usually present.
3. Patients who are seropositive for anti–LKM frequently are infected with hepatitis C virus. However anti- HCV may be falsely -positive in the setting of hypergammaglobulinemia, including that observed in patients with autoimmune hepatitis

Antibodies

Three types of autoimmune hepatitis have been recognized:

1. ***Type I***: it is the classic syndrome occurring in young women associated with marked hypergammaglobinemia and circulating antibodies such as:
   - ANA (in 80% of cases),
   - Anti-smooth muscle antibodies (ASMA) (in about 70% of cases).
   - Antimitochondrial antibodies (in about 15% of cases).
2. ***Type II:*** it is associated with anti-liver/kidney microsomal antibodies (anti-LKM). There is no ANA or ASMA. It mainly occurs in girls and young women.
3. ***Type III:*** it is associated with antibodies to soluble liver antigen/liver pancreas (anti- SLA/ LP).

Clinical Characteristics of Autoimmune Hepatitis

Clinical Features	Type 1	Type 2	Type 3
Diagnostic autoantibodies	ASMA ANA Antiactin	Anti-LKM	Soluble liver antigen
Age	Bimodal (10-20 y and 45-70 y)	Pediatric (2-14 y) Rare in adults	Adults (30-50 y)
Women (%)	78	89	90
Concurrent immune disease (%)	41	34	58
Gamma globulin elevation	+++	+	++
Low IgA*	No	Occasional	No
HLA association	B8, DR3, DR4	B14, Dr3, C4AQO	Uncertain
Steroid response	+++	++	+++
Progression to cirrhosis (%)	45	82	75

TREATMENT

Prednisolone 30 mg/d for 2 weeks followed by 20mg/daily, and again after 2 weeks a maintenance dose of 10-15 mg daily along with azathioprine 1-2mg/kg daily. Duration of treatment is unknown. Response rate to therapy is 80-90% but relapse rate is 50-90% if treatment is withdrawn.

Failure of aminotransferase level to normalize predicts lack of histologic resolution. Repeat biopsy should be done after 18-24 months.

ALCOHOLIC LIVER DISEASE

Ethanol (alcohol) is metabolized in the liver Acetaldehyde is formed by the oxidation of ethanol, which is responsible for the liver cell damage. Alcohol can produce a wide spectrum of liver disease from fatty liver to hepatitis and cirrhosis. The risk of developing alcoholic liver disease is related to amount of daily intake of alcohol. Usually 5-10 years of drinking is required to produce alcoholic cirrhosis. Steady daily intake is more hazardous than intermittent drinking.

1. Fatty liver

- Often asymptomatic
- Hepatomegaly
- Fibrosis around central hepatic veins may lead to cirrhosis of liver.

3. Alcoholic hepatitis

- In mild – moderate cases: mild jaundice with features of chronic liver disease. Liver biochemistry is deranged and diagnosis is made on liver biopsy and histology.
- In severe case: there is jaundice and ascites, abdominal pain & high-grade fever due to liver necrosis.
  On examination there is
  - Deep jaundice
  - Hepatomegaly
  - Splenomegaly (sometimes)
  - Ascites & ankle edema
  - Other signs of chronic liver disease.

3. Alcoholic cirrhosis

- Signs of chronic liver disease
- Diagnosis is confirmed on liver biopsy
- Usually the patient presents with one of the complications of cirrhosis.

INVESTIGATIONS

Blood CP

- Macrocytosis in the absence of anemia
- Leukocytosis or leukopenia
- Thrombocytopenia (10%)

LFTs

- Elevation of AST and ALT, however AST is greater than ALT at least twice or more.
- Bilirubin is increased
- Alkaline phosphatase is elevated but not more than 3 times of normal.
- *Serum gamma glutamyl transpeptidase (γ- GT) is elevated.*
- PT may be prolonged.
- Serum protein is low, gamma globulin is high.

Liver biopsy

It is diagnostic and shows macrovesicular fat, neutrophil infiltration, hepatic necrosis, Mallory bodies (alcoholic hyaline). Micronodular cirrhosis may be present as well.

MANAGEMENT

General measures

- *Abstinence from alcohol*
- *Nutritional support* to improve malnutrition; especially vitamins such as thiamine (B1) and folic acid. Glucose administration increases thiamine requirement and can precipitate Wernicke- Korsakoff syndrome; therefore thiamine should be given IV before glucose infusion.

Fatty change: Alcohol withdrawal reverses the condition

Alcohol hepatitis

- Treatment of ascites and encephalopathy
- Corticosteroid Methylprednisolone 32mg/d for 1 month may reduce short-term mortality in alcoholic hepatitis.

Alcoholic cirrhosis

Management of cirrhosis

CIRRHOSIS OF LIVER

Cirrhosis is an irreversible chronic parenchymal disease of liver resulting from the necrosis of liver cells followed by fibrosis and nodule formation. The liver architecture is diffusely abnormal and this interferes with liver blood flow (causing portal hypertension) and also interferes hepatic function (resulting in hepatic insufficiency).

ETIOLOGY

Common

- Chronic hepatitis due to hepatitis B, C and D viruses.
- Alcohol

Less common

Metabolic disease

- *Hemochromatosis*: Characterized by excessive deposition of iron in the liver.
- *Wilson's disease*: Characterized by excessive deposition of copper in the liver, mostly in young patients.
- *Alpha –1 antigrypsin deficiency*: results in cirrhosis and emphysema.
- *Cystic fibrosis*
- *glycogen storage disease*

Biliary obstruction

- *Primary biliary cirrhosis*
- *Secondary biliary cirrhosis* resulting from obstruction of bile duct due to stricture, stone or neoplasm.
- *Primary sclerosing cholangitis.*

Drugs

- Methyldopa, isoniazid, methotrexate.

Hepatic congestion

- *Cardiac failure:* causing backward pressure for a long period & leads to liver cirrhosis, this is called cardiac cirrhosis.
- *Budd-Chiari syndrome*: Characterized by venous outflow obstruction in hepatic vein, leading to congestion & cirrhosis.

Others

- Cryptogenic: cirrhosis of unknown etiology.
- Autoimmune hepatitis.

CLINICAL FEATURES

Non-specific

Initially the features are non-specific e.g.

- Weakness, fatigability, weight loss, muscle cramps.
- Anorexia, nausea and occasional vomiting
- Abdominal pain due to stretching of liver capsule because of hepatomegaly in early stages. Liver then becomes shrunken & hepatomegaly disappears.

Specific features

The clinical features of cirrhosis are mainly due to:

1. Portal hypertension
2. Hepatic insufficiency

CLINICAL FEATURES OF CIRRHOSIS

Portal hypertension	Hepatic insufficiency
• Splenomegaly • Hypersplenism • Collateral circulation causing variceal bleeding • Encephalopatyhy	• Jaundice • Palmar erythema and spider nevi • Endocrine abnormalities such as gynaecomastia, testicular atrophy, and amenorrhea • Bleeding tendency • Encephalopathy

PORTAL HYPERTENSION

- Portal hypertension results from destruction and distortion of the hepatic vasculature. It leads to obstruction of blood flow & increased backward pressure, resulting in hypertension in portal circulation.
- Normal portal vein pressure is 5-8 mmHg. Patients developing complications usually have portal pressure above 12 mmHg.
- On ultrasound maximum normal diameter of portal vein is 1cm, it becomes dilated in portal hypertension.
- The features of portal hypertension are <u>splenomegaly</u>, <u>hypersplenism</u>, <u>collateral circulation</u> and <u>ascites</u>.

Splenomegaly:

Splenomegaly is a cardinal finding, and a diagnosis of portal hypertension is unlikely when splenomegaly can not be detected clinically or by ultrasonography. Clinical splenomegaly is present in 35-50% of cases.

Hypersplenism

When spleen becomes enlarged its function of removing cells from circulation also increases, this is called hypersplenism. Moderate thrombocytopenia frequently occurs (platelet count around 100×10^9 / lit). Leukopenia occurs occasionally and anemia rarely.

By definition hypersplenism is characterized by:

- Splenomegaly
- Cytopenia (thrombocytopenia, granulocytopenia or pancytopenia)
- Normal bone marrow.

Collateral circulation

Increased portal vascular resistance leads to gradual reduction in the flow of portal blood to the liver and simultaneously to the development of collateral vessels, allowing the portal blood to bypass the liver and enter the systemic circulation directly. Collateral vessel formation is more prominent in the following areas:

- In the distal esophagus and proximal stomach: (esophagogastric varices).
- In the distal rectum and anus (causing hemorrhoids).
- On the anterior abdominal wall blood vessels radiate prominently from the umbilicus forming ***"caput Medusae"*** (rare).
- Renal, lumber, ovarian and testicular vessels.

The most important collateral vessels are the esophagogastric varices as they can cause bleeding which is usually severe and acute. Bleeding from rectum and anus is rare.

The presence of oesophagogastric varices is the diagnostic of portal hypertension.

Ascites

Accumulation of fluid in peritoneal cavity (ascites) in cirrhosis occurs due to two factors: portal hypertension and hepatic dysfunction.

Portal hypertension causes transudation of fluid in peritoneal cavity from the portal circulation (due to increased hydrostatic pressure), while the hepatic dysfunction causes ascites by three mechanisms.

1. Salt and water retention occurs as a result of peripheral arterial vasodilation and consequent reduction in effective blood volume. Nitric oxide is probably the vasodilator although prostaglandins and atrial natriuretic peptide may also be involved. The reduction in effective blood volume due to vasodilatation stimulates rennin- angiotensin system that promotes salt and water retention through stimulation of aldosterone. Failure of liver to metabolize aldosterone causes salt and water retention.

2. Liver is not able to synthesize sufficient proteins thus causing hypoalbuminemia, which results in decreased colloid osmotic pressure of the plasma resulting in leakage of fluid and development of edema and ascites.

3. Normally liver causes aldosterone metabolism, in case of hepatic dysfunction liver is unable to metabolize it, resulting in secondary hyperaldosteronism, and retention of sodium and water.

NON-CIRRHOTIC CAUSES OF PORTAL HYPERTENSION

Portal hypertension is always due to obstruction to portal blood flow somewhere in the portal venous system. Because portal venous system lacks valves, resistance at any level between right side of heart to splanchnic vasculature results in retrograde transmission of elevated pressure. Increased resistance can occur at three levels relative to hepatic sinusoids; presinusoidal, sinusoidal and postsinusoidal. Cirrhosis is the most common cause of portal hypertension but following conditions may also responsible.

Pre-sinusoidal obstruction

Portal vein thrombosis due to hypercoaguable states such as:

- – Polycythemia vera
- – Essential thrombocythemia
- – Deficiency of protein C, protein S and antithrombin III

- Malignant invasion from adjacent organ
- Abdominal trauma
- Biliary surgery

Sinusoidal obstruction

Sinusoidal obstruction due to distortion of the liver architecture is caused by:

- Cirrhosis
- Schistosomiasis
- Congenital hepatic fibrosis
- Myeloproliferative disease
- Primary biliary cirrhosis
-

Post-sinusoidal obstruction (rare) caused by:

- Budd-Chiari syndrome (hepatic vein thrombosis)
- Veno-occlusive diseases
- Right heart failure
- Constrictive pericarditis

Increased portal blood flow

Consequences of portal hypertension

1. Splenomegaly
2. Hypersplenism
3. Collateral circulation
4. Ascites (only when cirrhosis is present)

HEPATIC INSUFFICIENCY

In previous section we have discussed the features of portal hypertension, now we are discussing the second component i-e hepatic insufficiency. Following are the features of hepatic insufficiency.

1. Jaundice:

It is usually mild or absent. If occurs, it is mainly due to failure of bilirubin metabolism.

2. Circulatory changes:

These changes result from increased peripheral circulation (hyperdynamic circulation) causing the following manifestations:

Palmar erythema:

It is mottled redness of the thenar and hypothenar eminences due to increased peripheral blood flow.

Palmar erythema may also be present in normal old person, rheumatoid arthritis, pregnancy and thyrotoxicosis.

Spider nevi:

These are telangiectasia that result from arteriolar changes and comprise a central arteriole from which small vessels radiate. Spider nevi are confined to the area above the nipple and occur on the face, necklace area, forearms and dorsum of hands.

4. Endocrine abnormalities

- Gynecomastia develops because liver is unable to metabolize estrogen. It may also develop as a side effect of diuretic spironolactone that is commonly used in cirrhosis.
- Loss of libido
- Impotence and testicular atrophy in man
- Breast atrophy and amenorrhea in women

4. Hemorrhagic tendency

It occurs in advanced liver failure and is due to underproduction of coagulation factors. The manifestations of hemorrhagic tendency may be

- Bruising, purpura
- Epistaxis

- Menorrhagia (some patients present with this problem only and then diagnosed as a case of cirrhosis).
- GIT bleeding

5. Skin changes

- Pigmentation occurs in cirrhosis (especially caused by hemochromatosis) and cirrhosis due to any reason as a result of cholestasis.
- Clubbing of fingers and toes may also present.

6. Dupuytren's contracture

Associated with alcoholic cirrhosis and is very rare.

7. Hepatic encephalopathy

The cerebral disturbance or encephalopathy develops due to the following two factors:

- Collateral venous circulation in cirrhosis bypasses the liver and allows nitrogenous substances from the gut to reach the systemic circulation through which they reach to the brain directly and produce cerebral disturbance.
- Liver is responsible for detoxification of substances. When there is severe loss of liver function the un-detoxified substances such as ammonia reach to the brain, and produce cerebral dysfunction.

Features of encephalopathy are from restlessness, aggressive outbursts and drowsiness to coma. It is discussed thoroughly in the next sections.

8. Renal failure (hepatorenal syndrome)

renal failure develops in advanced cirrhosis mostly with ascites. It is caused by decreased effective blood volume and hypotension as a result of vasodilatation due to release of nitric oxide from the liver. Details are given in the section of complications of ascites.

9. Hepatopulmonary syndrome

In cirrhosis pulmonary arteriovenous shunts also develop, leading to hypoxia and eventually central cyanosis, this is called hepatopulmonary syndrome.

DIFFERENTIAL DIAGNOSIS OF CIRRHOSIS

1. D/D of one type of cirrhosis from another type
2. D/D of hepatomegaly (in initial stages).
3. D/D of splenomegaly
4. D/D of ascites
5. D/D of hematemasis
6. D/D of encephalopathy

IMPORTANT CLINICAL FEATURES OF CIRRHOSIS

1. ***Portal hypertension presents with***
   - Splenomegaly
   - Hypersplenism
   - Collateral circulation – Varices
   - Ascites
2. ***Hepatic insufficiency***
   - Jaundice
   - Palmar erythema, spider nevi
   - Endocrine abnormalities
   - Gynaecomastia (gynecomazia)
   - Impotence and testicular atrophy in men.
   - Loss of libido
   - Breast atrophy and irregular menses in women.
   - Hemorrhagic tendency
     Brusing, purpura, epistaxis, menorrhagia, GIT bleeding.
   - Skin pigmentation, clubbing
   - Hepatic encephalopathy
   - Hepatorenal syndrome
   - Hepatopulmonary syndrome

INVESTIGATION IN CIRRHOSIS

LFTs

- Serum aminotransferases (ALT & AST) and alkaline phosphatase are slightly elevated
- Serum albumin is reduced
- Serum globulin is raised therefore the albumin globulin ratio (A/G ratio) is disturbed – the reason of increasing globulin is that albumin is completely synthesized by the liver while 20-40% of globulin is also formed in the lymphoid tissue. Therefore due to liver dysfunction albumin synthesis is decreased while the globulin synthesis continues in the lymphoid tissues.
- Prothrombin time becomes prolonged
- Serum bilirubin may be normal or slightly raised

Serum electrolytes
Low serum sodium indicates severe liver disease. Hyponatremia is dilutional secondary to a defect in free water clearance (dilutional hyponatremia). Hyponatremia may be due to excessive diuretic therapy.

Blood C/P
- Anemia due to hypersplenism or blood loss.
- WBC count may be decreased due to hypersplenism or increased due to infection or may be normal.
- Platelet count is usually low due to hypersplenism.

Imaging
Ultrasound of upper abdomen may reveal:
- Cirrhotic changes in liver
- Portal vein dilatation
- Splenomegaly

Endoscopy: Esophagogastroscopy to confirm presence of varices and portal hypertensive gastropathy.

Liver biopsy
Liver biopsy is necessary to confirm the severity and type of liver disease.

To identify the cause
- Viral markers
- Serum autoantibodies.
- Serum immunoglobulins
- Serum ceruloplasmin and urinary copper for Wilson's disease.
- Serum alpha 1- antitrypsin should always be done in young cirrhotics.
- Serum iron, ferritin and total iron binding capacity should be performed to exclude hemochromatosis.

Alpha-fetoprotein: if more than 400ng/ml is strongly suggestive of hepatocellular carcinoma.

MANAGEMENT
There is no treatment that will arrest or reverse cirrhotic changes. Therefore, the management is only of the complications.

PROGNOSIS
Prognosis depends on etiology, presence of complications and stage at which the diagnosis is made.
There are two prognostic score systems
- Child – Pugh classification
- Model for End- Stage Liver Disease (MELD).

Hematemesis, jaundice, and ascites are unfavorable signs. Serum bilirubin > 3mg/dl, serum albumin < 3gm/dl, PT >6 seconds over the control, ascites, hepatic encephalopathy and upper GI bleeding suggests 50% survival rate in 6 months.

Modified Child-Pugh classification for prognosis of cirrhosis

	Numerical score		
Parameters	**1**	**2**	**3**
Ascites	None	Mild	Moderate to severe
Encephalopathy	None	Mild to moderate	Moderate to severe
Serum bilirubin (mg/dl)	<2	2-3	>3
Serum albimin (g/dl)	>3.5	3-3.5	<3
Prothrombin time (seconds increased over control)	<4 sec	4-6 sec	>6 sec

Total numerical score	Child-Pugh class	Survival %		
		1 year	5 years	10 years
<7	Class A	82	45	25
7-9	Class B	62	20	7
10+	Class C	42	20	0

The survival for Child's classification C is < 12 months.

POOR PROGNOSTIC FACTORS

Blood tests

- Low albumin (< 2.5mg/d/l)
- Low serum sodium (< 120 mmol L)
- Prolonged prothrombin time

Clinical

- Persistent jaundice
- Failure of response to therapy
- Ascites
- Hemorrhage from varices, particularly with poor liver function
- Hepatic encephalopathy
- Small liver
- Persistent hypotention
- Etiology, e.g. alcoholic cirrhosis (if the patient continues drinking).

COMPLICATIONS OF CIRRHOSIS

1. Variceal hemorrhage
2. Ascites
3. Hepatic encephalopathy
4. Renal failure
5. Hepatoma

VARICEAL HEMORRHAGE

The collaterals at esophagogastric junction (known as varices) are superficial in position and tend to rupture. Bleeding is likely to occur in 1/3 patients with varices, particularly those with large varices, high pressure and more severe liver disease. Mortality rate is 50%.

CLINICAL FEATURES

Patients of variceal bleeding present with painless but massive hematemesis with or without melena. Other causes of bleeding such as peptic ulcer, portal hypertensive gastropathy and gastritis should also be considered. Patient may be hypovolemic and may manifest with hypotension to shock. Examination for signs of chronic liver disease should be performed.

Experience sharing: Upper GI bleeding is a common emergency, proper history and examination is required to differentiate bleeding from varices or some other cause. In the absence of previous history presence of splenomegaly, reduced liver span and prolonged PT usually suggest variceal bleed.

INVESTIGATIONS

- Blood CP (CBC) to measure the initial level of hemoglobin and platelet count.
- PT, APTT.
- LFTs
- Serum electrolytes

MANAGEMENT

PREVENTION OF FIRST EPISODE OF VARICEAL BLEEDING (prophylactic measures)

Non-selective beta-blocker such as propranolol reduces the risk of first episode of bleeding, Isosorbide mononitrate can be used in patients who do not tolerate beta-blocker. Propranolol is also the best treatment of congestive gastropathy.

Prophylactic sclerotherapy is not indicated, it increases mortality. However banding in high risk patient can reduce the incidence of first episode of bleeding.

MANAGEMENT OF ACTIVE BLEEDING

INITIAL RESUSCITATION

- Monitor blood pressure and pulse.
- Pass I/V canulla and give plasma expander (e.g. Haemaccel or Gelafundin) to restore circulation and arrange for blood and blood products such as fresh frozen plasma.
- Fresh frozen plasma (FFP) should be administered if PT is > 1.5 times normal (at least 7-14 FFPs are required to stop bleedings).
- Platelets should be infused if count is less than 50,000/μL.
- Pass nasogastric (N/G) tube to evacuate the stomach to reduce nausea and vomiting and to monitor ongoing bleeding.

URGENT ENDOSCOPY

Urgent endoscopy is performed after the patient becomes hemodynamically stable that usually takes 2-12 hours. Endoscopic examination is performed:

- To exclude other causes of upper GI bleeding such as peptic ulcer or congestive (portal hypertensive) gastropathy.

- For acute endoscopic treatment of varices with either banding or sclerotherapy.

Banding

- Varices are sucked and a rubber band is dislodged over the varices.
- Repeat banding sessions are performed at interval of 1-2 weeks until the varices are obliterated.
- Banding achieves lower rates of rebleeding, complications and death than sclerotherapy and is the endoscopic treatment of choice.

Injection sclerotherapy:

- The varices are injected with sclerosing agent (ethanolamine tetradecyl sulfate) that arrests bleeding by producing vessel thrombosis. A needle is passed down the biopsy channel of the endoscope and a sclerosing agent is injected into the varices.
- A repeat session is performed at 3-7 days, followed by sessions at 1-3 week intervals, until the varices are obliterated.
- Complications of sclerotherapy are chest pain, fever, bacteremia, esophageal ulceration, perforation and stricture.

PHARMACOLOGICAL THERAPY
(TO REDUCE PORTAL PRESSURE)

Urgent endoscopy facilities are not available in majority of our medical centers and we usually rely on resusucitation and pharmacological therapy such as octreotide.

Vasconstrictor therapy

The vasoconstrictor drugs are used for emergency control of bleeding by constricting the splanchnic arterioles and thereby reducing portal pressure and blood flow. Octereotide is the treatment of choice while vasopressin can also be used.

Octreotide

Octreotide is somatostatin analog that reduces the splanchnic and hepatic blood flow and portal pressure in the cirrhotic patients. Octreotide provides acute control of variceal bleeding in up to 80% of patients and may be comparable in efficacy to sclerotherapy. It is also superior to vasopressin in control of variceal bleeding and is without significant side-effects because it is more selective to splanchnic vasculature while vasopressin is non - selective and causes vasoconstriction all over the body that may aggravate ischemic heart disease.

Dose: Octreotide (Inj. Sandostatin) 50 µg (0.05 mg) I/V bolus followed by 50 µg/h in infusion form. Continue therapy for 5 days (cost of one injection of Sandostatin is about Rs. 250).

Vasopressin

- Vasopressin is a nonselective vasoconstrictor and reduces splanhnic blood flow.
- Dosage: Vasopressin (Inj. Pitressin 20 units in 200 ml of dextrose water over 20 minutes (i.e. 150 drops/min), this may be repeated 3-4 times at hourly intervals as drug is destroyed rapidly. It controls bleeding in 50% of cases.
- Abdominal colic, evacuation of bowles and facial pallor indicate that vasopressin is active otherwise suggest an inert preparation.
- Complications of vasopressin: angina, arrhythmia & even myocardial infarction. Therefore it should be avoided in patients with ischemic heart disease. Nitrates by sublingual, intravenous or patch route reduce the cardiac complications of vasopressin when used concomitantly.

OTHER MEASURES TO STOP BLEEDING

Balloon tamponade:

- It is used when sclerotherapy has failed or unavailable, or if vasoconstrictor therapy has failed or is contraindicated.
- The Sangstaken-blackmore tube is passed into the stomach and the ballon is inflated with air and pulled back which exerts pressure on the lower esophagus and gastric fundus to stop bleeding. The tube should be left in place for up to 12 hours and removed in the endoscopy room prior to sclerotherapy. Successful rate is 90% in controlling variceal bleeding.

Complication: aspiration pneumonia, esophageal rupture and mucosal ulceration.

Transjugular intrahepatic portocaval shunt (TIPS)

- TIPS is performed when bleeding can not be stopped with pharmacologic and endoscopic therapy.
- In this technique, a guidewire is passed from the jugular vein into the liver and an expandable metal stent is forced over it into the liver substance to form a portosystemic shunt between portal and hepatic vein. It can control bleeding in 90% of cases. There is no need of general anesthesia.
- Stent stenosis or thrombosis is major complication.

Emergency surgery

Emergency surgery is performed when other measure fail or if TIPS is not available, particularly if bleeding is from gastric fundal varices. Esophageal transection and ligation of feeding vessels to the bleeding varices is the most common surgical technique.

Additional management of acute episode

Lactulose

Encephalopathy can be precipitated by large bleed (since blood contains protein). To prevent encephalopathy, lactulose (Duphalac) 30ml 6 hourly is given which prevents synthesis of ammonia from protein. It produces diarrhea, therefore washing the blood from GIT.

Vitamin K

In cirrhotic patients with prolonged PT, vitamin K (10mg) should be given intravenously slowly in the hope that it will help in the synthesis of coagulation factors by the functioning parts of liver.

PREVENTION OF REBLEEDING

Once the initial episode of bleeding is controlled, the risk of rebleeding is 60-80% without further therapy. The highest incidence of rebleeding is in the first 6-weeks.

Following are the measures to prevent rebleeding:

Long term injection sclerotherapy or banding.

Repeated course of banding or sclerotherapy at weekly intervals may be used to obliterate varices (usually 4-6 treatment sessions are required). Between 30-40% of varices return per year, so the follow up endoscopy should be performed.

Beta-blockers and nitrates

None-selective beta-blocker such as propranolol (Inderal) is effective in reducing the incidence of rebleeding from varices and also from portal congestive gastropathy. Start with 20mg twice daily and gradually increase dose until the heart rate falls by 25% or reaches 55 beats/min.

Long-acting nitrates are also effective in reducing incidence of rebleeding and are used in patients who cannot tolerate beta-blocker such as asthmatics. Start with isosorbide mononitrate (Monis) 10mg daily and gradually increase to 20-40mg twice daily. Beta-blocker and nitrate may be given in combination.

Portosystemic shunt

Portocaval or distal splenorenal shunt reduces the incidence of rebleeding but the chances of encephalopathy increase due to entrance of nitrogenous substances into systemic circulation bypassing the liver.

Liver transplantation

Liver transplantation is discussed later in detail.

MANAGEMENT OF VARICEAL BLEEDING

Prevention of first episode

- Propranolol or isosorbide mononitrate
- Banding of large varices.

Measure to stop active bleeding episode

- Plasma expanders, blood, FFPs, platelets.
- Octereotide
- Endoscopic banding or sclerotherapy
- Ballon tamponade
- TIPS
- Lcactulose and vitamin K

Measures to stop rebleaing

- Repeated banding or sclerotherapy
- Beta-blockers or nitrates
- Shunts

Liver transplantation

ASCITES

Pathological accumulation of fluid in peritoneal cavity is known as ascites. It is a common complication of cirrhosis of the liver.

PATHOGENESIS

The mechanism of formation of ascites in liver cirrhosis is as following:

- *Sodium and water retention* occurs due to stimulation of rennin-angiotensin system that develops as a result of low perfusion pressure of the kidney in cirrhosis. This retained fluid causes portal hypertension and ultimately ascites. Nitric oxide has been postulated as a vasodilator (causing low perfusion pressure), although other substances such as prostaglandins and atrial natriuretic peptide may be involved.

- *Portal hypertension* exerts a local hydrostatic pressure resulting in transudation of fluid in peritoneal cavity.

- *Low serum albumin,* as a result of poor synthesis by the liver reduces plasma osmotic pressure and resulting in transudation of fluid in peritoneal cavity.

DIFFERENTIAL DIAGNOSIS OF ASCITES

In long or short case of ascites, etiology of chronic liver disease should be looked clinically by finding signs of all conditions that may be responsible for it. In one exam student got case of ascites with underlying nephrotic syndrome; there were no associated features of nephrotic syndrome. In such condition it is better to give differential diagnosis.

Practically after history and examination we perform diagnostic tap of ascitic fluid and send it to laboratory. According to lab. report causes of ascites may be divided into the conditions that produce transudate or exudates. However recently causes of ascites are divided according to the Serum- Ascites Albumin Gradient (SAAG). It is the difference between serum albumin and ascitic fluid albumin. SAAG more than 1.1 g/dl strongly suggests that the cause of ascites is portal hypertension. SAAG less than 1.1 g/dl indicates non-portal hypertensive cause.

TRANSUDATE AND EXUDATE

Ascitic fluid may be exudates or transudate depending upon the protein content. Following are the common causes of exudates and transudate ascitic fluid.

Transudate (protein < 2.5 g/dl)

1. Portal hypertension: *due to*
   - Cirrhosis (most common)
   - Fulminant hepatic failure
   - Alcoholic hepatitis
   - Congestive heart failure
   - Constrictive pericarditis

2. Hypoalbuminemia: *due to*
   - Nephrotic syndrome
   - Protein losing enteropathy
   - Severe malnutrition

Exudate (protein> 2.5g/dl)

Infections: tuberculous peritonitis, bacterial peritonitis.

Malignancy: hepatic or peritoneal.

CAUSES OF ASCITES ACCORDING TO SAAG

Ascites when SAAG is > 1.1 g/dl

1. Portal hypertension (transudate)
   - Cirrhosis
   - Chronic hepatic congestion
     - Right-sided heart failure
     - Constrictive pericarditis
     - Budd-Chiari syndrome
2. Myxedema
3. Nephrotic syndrome

Ascites when SAAG is < 1.1 g/dl

1. Hypoalbuminemia (transudate).
2. Infections pyogenic or tuberculous (exudates)
3. Malignancy (exudates)
4. Nephrotic syndrome (transudate)

CAUSES OF ASCITES ACCORDING TO THE TYPE OF ASCITIC FLUID

Straw-colored	Chylous / Hemorrhagic
• Malignancy • Cirrhosis • Infective Tuberculosis Primary or secondary peritonitis • Hepatic vein obstruction (Budd-Chiari syndrome) • Chronic pancreatitis • Congestive cardiac failure • Constrictive pericarditis • Meigs' syndrome • Hypoproteinaemia,	**Chylous** Obstruction of main lymphatic duct (e.g. by carcinoma) – chylomicrons are present **Hemorrhagic** Malignancy Ruptured ecotopic pregnancy Abdominal trauma Acute pancreatitis

CLINICAL FEATURES OF ASCITES

- Abdominal distension with fullness in the flank
- Diffuse abdominal pain
- Features of cause (most common cause is chronic liver disease).

On examination

1. Eversion of umbilicus

2. *Fluid thrill:* when a huge ascites is present, a fluid thrill is elicited by flicking one side of the abdomen with index finger and feeling the vibration on the other side of the abdomen with palmer surface of other hand. Thrill is also conducted through fat; to rule out this, another person or patient is asked to place the ulnar side of his hand in the middle of the abdomen vertically.

3. *Shifting dullness:* it is a dull area which moves or changes shape when the patient changes position. Ascites is suggested by presence of dullness in the flanks with central abdominal resonance. Start percussion from center of abdomen towards the flank till the percussion note becomes dull. Keep the hand there and ask the patient to roll on the other side and percuss again, now the percussion note will be resonant as under the effect of gravity the fluid moves to the lower flank Now percuss again towards umbilicus to obtain dull note.

INVESTIGATIONS

ASCITIC FLUID ANALYSIS

Diagnostic paracentesis:
Approximately 10-20 ml fluid is removed for diagnostic studies.

1. Inspection of ascitic fluid

Cause	*Appearance*
• Cirrhosis	• Clear, straw-colored or light green
• Malignant disease	• Bloody
• Infection	• Cloudy
• Biliary Communication	• Heavy bile staining
• Lymphatic Obstruction	• Milky white (chylous)

2. Cell count

- Normal ascitic fluid contains WBC < $500/mm^3$ and neutrophils < $250/mm^3$
- Neutrophil count more than $250/mm^3$ strongly suggest bacterial peritonitis whether spontaneous bacterial peritonitis (SBP) or secondary peritonitis due to perforation of abdominal viscus or appendicitis).
- Elevated WBC with predominance of lymphocytes arouses suspicion of abdominal tuberculosis or peritoneal carcinomatosis.

3. Albumin and total protein

- The serum-ascites albumin gradient (SAAG) is the best single test that can classify ascites into caused by portal hypertension by non-portal hypertension.

- SAAG > 1.1 g/dl strongly suggests underlying portal hypertension while SAAG < 1.1 g/dl implicates non-portal hypertensive cause.
- The accuracy of SAAG is more than 95%. In about 4% patients there is mixed ascites due to portal hypertension and malignancy, thus high SAAG is indicative of portal hypertension but does not excludes concomitant malignancy.
- Ascitic fluid protein less than 1 g/dl predispose the patient to spontaneous bacterial peritonitis.

4. Culture and gram stain

To identify infection ascitic fluid culture is performed. About 5-10 ml of ascitic fluid is incculated in blood culture bottle at the patient's bedside. Inoculation at bedside increase sensitivity of positive culture over 85% in patients with neutrophil count >250/mm^3 compared with routine culture in which sensitivity is 50%.

5. Other tests

- RBC > 50,000 / µ L denotes hemorrhagic ascites which usually is due to malignancy, tuberculosis or trauma.
- A pH less than 7 suggests bacterial infection.
- Cytology for malignant cells.
- Glucose – low in T.B. peritonitis
- Amylase – high amylase in pancreatic ascites.

ULTRASOUND ABDOMEN

It confirms presence of ascites, and distinguishes between portal and non-portal causes of ascites. It also shows liver architecture, size of portal vein.

LAPROSCOPY

It is an important test in the evaluation of some patients with non-portal hypertensive ascites, it permits direct visualization and biopsy of the peritoneum, liver, and some intra-abdominal lymph nodes.

LONG CASE OF ASCITIC PATIENT

History

Following questions are helpful in the diagnosis of ascites and should be included in history.

- Chronic liver disease: any predisposing factor such as history of previous jaundice, transfusion, operations, alchol intake, exposure and contact with patient of chronic liver disease. Features of autoimmune hepatitis.
- Abdominal tuberculosis: history of fever of long duration, weight loss, anorexia, sweating, features of pulmonary tuberculosis such as cough chest pain and hemoptysis. Previous treatment of tuberculosos.
- Malignancy: weight loss, resistant ascites.
- Nephrotic syndrome related questions.
- Cardiac failure and constrictive pericarditis related questions.

Examination

- Look for anemia, jaundice, clubbing, palmar - erythema, spider nevi, gynecomastia, and testicular atrophy.
- Lymph node in left supraclavicular fossa for intra-abdominal malignancy.
- Raised JVP for right-sided heart failure.
- Abdominal palpation for tenderness and hepatosplenomegaly, fluid thrill, shifting dullness.
- Examine respiratory system for evidence of tuberculosis, such as pleural effusion.

Investigations

- Blood CP
  - Anemia due to hypersplenism, blood loss or anorexia.
  - High WBC count indicates peritonitis.
  - Platelets may be low due to hypersplenism.
- Ascitic fluid analysis
  - Calculate SAAG
  - Look neutrophil count, amount of protein, glucose.
- Ascitic fluid gram staining and culture.
- LFTs, PT, serum protein with A/G ratio.
- X-ray chest for the evidence of pulmonary tuberculosis.
- Ultrasound abdomen for hepatic architecture (coarse in cirrhosis), hepatic metastasis, portal vein dilatation, intra-abdominal lymph adenopathy.

MANAGEMENT

GENERAL MEASURES

- Daily monitoring of vital, weight, abdominal girth and urine output.
- *Dietary modifications*
  Sodium restriction to 1g/day (2g of sodium chloride)
  Water restriction to 1 liter/day.
- *Bed rest:*
  Bed rest improves renal perfusion & may lead to diuresis.

SPECIFIC MEASURES

Diuretics

- Spironolactone (Tab. Aldactone 100mg) is a potassium sparing diuretic and is the diuretic of first choice.
  - Mode of action: spironolactone antagonizes the aldosterone and prevents salt and water reabsorption from the kidney, as secondary hyperaldosteronism is a major factor in salt and water retention in cirrhosis.
  - Start with 25 mg four times daily and increase as needed by 100mg/day every several days to a maximum dose of 400mg/d.
  - Spironolactooe is available by the name of Tab. Aldactone 25mg and 100mg.
  - Main side-effects of spironolactong are hyperkalemia and gynnecomastia. If the patient do not tolerate spisonolactone due to gynecomastia another potassium sparing agent such as amiloride may be used.

- Frusemide (Lasix 20-80 mg/d) is a high potency loop diuretic and should be added if response to high doses of spironolactone alone is poor. Main side effects are hyponatremia, hypokalemia and volume depletion.

A combination of spironolactone (50 mg) and frusemide (20mmg) is available by the name Spiromide . Another combination of frusemide (40 mg) and amiloride (5 mg) is available by the name of Lasoride.

The goal of daily weight loss should be 0.5 kg if only ascites is present and 1 kg if ascites and edema both are present.

Therapeutic paracentesis

In patients with massive ascites causing respiratory distress, or ascites refractory to diuretic therapy, large volume paracentesis (4-6 L) over 1-2 hours is effective.

However main danger of this approach is the production of hypovolemia as the ascitic fluid re- accumulates at the expense of circulating volume leading to shock. The problem can be overcomed by administration of salt-free albumin concomitantly at a dosage of 10 g/L of ascitic fluid removed to protect the intravascular volume. Salt free albumin is available by the name of Inj. Albumin Human 20% It is available in two quantities; 50ml infusion (containing 10g albumin and costs about Rs. 3000 and 100 ml infusion containing 20g albumin and costs about Rs. 6000).

If the patient is non-affording then use plasma expanders such as gelatin infusion (Gelafundin) 125 ml per liter of ascitic fluid removed.

LeVeen Shunt and TIPS

LeVeen shunt is a procedure in which a catheter is introduced from the peritoneal cavity (subcutaneously) to the internal jugular vein, incorporating a one-way valve & allowing the passage of ascitic fluid directly into the circulation. This procedure is effective in resistant ascites, but complications such as tube blockage, infection, superior vena caval thrombosis, pulmonary edema, bleeding from esophageal varices and DIC limit its use.

Transjugular intrahepatic portosystemic shunt (TIPS) can also relieve resistant ascites and is better to LeVeen shunt.

SPONTANEOUS BACTERIAL PERITONITIS (SBP)

Patients with cirrhosis are very prone to infection. Spontaneous bacterial peritonitis is a complication of ascites occurring in about 8% of cirrhotics with ascites.

Predisposing factors

- Very advanced liver disease.
- Ascitic fluid albumin has opsonization property and normally provides some protection against bacteria. Low ascitic fluid albumin (1 g/dl or less) predisposes the patient to infection.

Source of infection

- Most bacteria contributing to SBP are believed to gain access to the peritoneum by hematogenous route. E Coli is the most common organism; others are klebsiella and entercococci.

Clinical features

Typical features include abrupt onset of fever, chills, generalized abdominal pain and rebound abdominal tenderness. However clinical features may be minimal and some patients manifest only worsening jaundice or encephalopathy in the absence of abdominal complaints and fever.

Diagnosis

Ascitic fluid WBC count more than 500 cell/ mm^3 (with a proportion of neutrophil of 50% or more) or the neutrophil count more than 250/mm^3 suggests bacterial peritonitis while the results of ascitic fluid culture are pending. Ascites culture in blood culture bottle inoculated at patient's bedside gives the highest yield of organisms.

The presence of more than 10,000/ mm^3 WBCs, multiple organisms or failure to improve after standard therapy for 48 hours suggest the secondary peritonitis due to rupture of abdominal viscus, not due to SBP.

Treatment

Empirical therapy should be started with third generation cephalosporin such as cefotaxime (Inj. Claforan) 2g i.v. 8-hourly for at least 5 days. It can be changed according to culture and sensitivity report later.

Response to therapy can be documented by a decrease in the neutrophil count of at least 50% on repeat paracentesis 48 hours after initiation of therapy.

Prophylaxis

Recurrent episodes of SBP are common; at least 70% patients get another episode within a year of first episode. Therefore prophylactic antibiotic therapy may be used such as cirpofloxacin 750mg (Tab. Ciproxin available in 250 and 500mg) once weekly or norfloxacin (Tab. Noroxin) 400mg daily or co-trimoxazole (Tab. Septran) 5 days a week may be effective.

HEPATIC ENCEPHALOPATHY

Hepatic encephalopathy is a state of disordered CNS function resulting from failure of liver to detoxify toxic agents of gut origin because of hepatocellular dysfunction and portosystemic shunting. The blood bypasses the liver via the collaterals and the toxic metabolites (e.g. ammonia, free fatty acids and mercaptan) pass directly to the brain to produce the encephalopathy. There is also an increased sensitivity of CNS neurons to the inhibitory neurotransmitter (GABA) and an increase in circulating levels of endogenous benzodiazepines. Cerebral edema is frequently present and contributes to the development of clinical features.

PRECIPITATING FACTORS

- Gastrointestinal bleeding is the most common precipitating factor, which leads to an increase in the production of ammonia and other nitrogenous substances which are then absorbed.
- Increased dietary protein may precipitate encephalopathy as a result of increased production of nitrogenous substances by colonic bacteria.
- Electrolyte disturbance, particularly hypokalemia causes systemic alkalosis that causes an increase in the amount of nonionic ammonia (NH_3) which is neurotoxic and readily crosses blood- brain barrier and

accumulate in the brain. Hypokalemic alkalosis inhibits the conversion of ammonia (NH_3) into ammonium ion (NH_4) that is non-toxic. Increased NH_3 leads to encephalopathy. Hypokalemia also directly stimulates renal ammonia production. Hypokalemia is a common precipitating factor and usually results from excessive use of diuretics, vigorous paracentesis and vomiting.

- Infection is also very common precipitating factor especially SBP.

COMMON PRECIPITATING FACTORS OF HEPATIC ENCEPHALOPATHY

Increased Nitrogen Load
- Gastrointestinal bleeding
- Excess dietary protein
- Azotemia
- Constipation

Electrolyte and Metabolic Imbalance
- Hypokalemia
- Alkalosis
- Hypoxia
- Hyponatremia

Drugs
- Narcotics, tranqualizers, sedatives
- Diuretics

Miscellaneous
- Infection
- Surgery
- Portosystemic shunt
- Superimposed acute liver disease
- Progressive liver disease.

CLINICAL FEATURES

Symptoms

- Disturbance of sleep with sleeping during day and awaking in night is one of the earliest features.
- Alteration in personality, mood disturbances, confusion, deterioration of self-care and deterioration in handwriting, slurring of speech, disorientation, drowsiness and eventually coma develop. Convulsions sometimes develop.
- Hyperventilation, fever, nausea, vomiting are common.

Signs

- Fetor hepaticus – a sweat smell to the breath due to mercaptans.
- Flapping tremor or asterixis is a non-rhythmic asymmetric lapse in voluntary sustained position of limb, head and trunk. It is best demonstrated when the patient extends the arms and dorsiflexes the hands.
- Constructional apraxia: patient is unable to do the already learnt things such as write or draw a five-pointed star.

CLINICAL STAGES OF HEPATIC ENCEPHALOPATHY

Stage	Mental Status	Asterixis (Flapping tremor)	EEG
I.	Euphoria or depression, mild confusion, slurred speech, disordered sleep	+ / -	Usually normal
II	Lethargy, moderate confusion.	+	Abnormal
III	Marked confusion, incoherent speech, sleeping but arousable.	+	Abnormal
IV	Coma; initially responsive to noxious stimuli later unresponsive	–	Abnormal

INVESTIGATIONS

Diagnosis of hepatic encephalopathy is usually of clinical if acute or chronic liver disease is evident, no confirmatory test is available, however the following investigations help in the diagnosis of hepatic encephalopathy:

- Liver biochemistry such as LFTs, PT, Serum albumin---- to confirm the presence of liver disease.
- EEG: shows diffuse slowing of the normal alpha waves with eventual development of delta waves. Visual evoked potential also detect subclinical encephalopathy.
- Arterial blood ammonia: elevated level of arterial blood ammonia is highly suggestive of diagnosis in the presence of clinical features of hepatic encephalopathy. However ammonia may be elevated in the absence of encephalopathy, therefore it is not diagnostic test, it is helpful when clinical features are present and ammonia is found elevated.

DIFFERENTIAL DIAGNOSIS

- Sedative overdose
- Acute alcoholic intoxication
- Subdural hematoma
- Meningitis
- Hypoglycemia
- Metabolic encephalopathies

MANAGEMENT

1. Identify and remove the precipitating factor.
2. Stop or reduce diuretic therapy.
3. Correct any electrolyte imbalance.
4. Lowering of blood ammonia levels by decreasing the absorption of protein and nitrogenous products from the intestine by the following measures:
   - Protein free diet
   - Give purgatives in order to empty the bowels of nitrogenous substances.
   - Luctulose is an osmotic purgative that removes blood (in case of GI bleeding) and other nitrogenous substances from the gut. It also reduces the colonic pH that inhibits ammonia absorption. Lactulose (Duphalac) is started with 30ml 3-4 times daily (even hourly until diarrhea occurs) and then adjust so that the patient has 2-3 soft stools per day. Constipation should always be avoided.
   - The ammonia producing intestinal flora may be controlled with Tab. Neomycin 1g oral 6 hourly. However neomycin may cause toxicity and other safe drugs can be used such as metronidazole (Flagyl) 250mg orally 3-times daily or Vancomycin 1g orally twice daily.
5. Treat any infection such as SBP, UTI, pneumonia etc.
6. Flumazenil, a benzodiazepine receptor antagonist, can induce a transient improvement.

Long term

- Protein should be reduced to 20-50g/day
- Avoid constipation
- Duphalac 10-30 cc TDS
- Avoid precipitating factors e.g. over diuresis & narcotic drugs.

HEPATORENAL SYNDROME (renal failure)

Hepatorenal syndrome is a renal failure in the absence of shock in patient with end – stage liver disease in whom renal function fails to improve following IV infusion of 1.5 liter saline. Renal failure occurs typically in a patient with advanced cirrhosis with jaundice and ascites. It presents as low urine output, raised urea and creatinine, hyponatremia, low urinary sodium and hypotension. Kidneys are histologically normal and can work normally if transplanted to non- cirrhotic person (i-e it is a pre- renal type renal failure). Hepatorenal syndrome should be diagnosed only when other causes of renal failure are excluded.

Type I hepatorenal syndrome is characterized by doubling of serum creatinine to a level greater than 2.5 mg/dl in less than two weeks. Type II is more slowly progressive and chronic.

Pathogenesis

Hepatorenal syndrome in cirrhosis develops due to reduced blood flow as a result of low peripheral resistance. This is due to secretion of

nitiric- oxide. The reduced blood flow leads to increased secretion of vasoconstrictors such as noradrenaline, angiotensin, aldosterone and vasopressin that cause vasoconstriction of renal vasculature resulting in reduced GFR that leads to extremely low sodium excretion (< 5 mmol/L), salt water retention and renal failure. There may be decreased production of renal vasodilators such as prostaglandin E^2.

Precipitating factors
Overvigorous diuretic therapy, diarrhea, GI bleeding, sepsis and large paracentesis are common precipitating factors.

Management
The patient should be treated for pre- renal failure. Diuretic should be stopped and intravascular hypovolemia is corrected with salt free albumin. Dopamine infusion is ineffective. TIPS may improve the condition. Overall prognosis is poor. Liver transplantation is the best option.

HEPATOPULMONARY SYNDROME

Hepatopulmonary syndrome occurs in chronic liver disease and manifests as dyspnea in the upright position (orthodeoxia) that is relieved by recumbency.

Pathogenesis
Hypoxia and dyspnea develops due to right to left intrapulmonary shunt due to dilatation of intrapulmonary vessels, because liver is unable to clear circulatory pulmonary vasodilators.

Investigations
- Pulse oximetry shows oxygen saturation less than 92%.
- Contrast echocardiography is a sensitive screening test for detecting intrapulmonary shunts.
- Macroaggregated albumin lung perfusion scanning is more specific and is used to confirm the diagnosis.
- High resolution CT scan of chest may show dilated pulmonary vessels.

Management
No specific treatment is available, however IV methylene blue may improve oxygenation in patients by inhibiting nitric oxide – induced vasodilatation. TIPS may provide palliation in patients awaiting liver transplantation.

BILIARY CIRHOSIS

Biliary cirrhosis results from prolonged biliary obstruction anywhere between the small interlobular bile ducts and papilla of Vater.

Types:
There are two types of biliary cirrhosis:
- Primary
- Secondary

PRIMARY BILIARY CIRRHOSIS
Primary biliary cirrhosis is a chronic disease of liver in which small interlobular bile ducts of the liver become progressively damaged and eventually leading to cirrhosis and cholestasis. Women are affected in 90% of cases in the age range 40-50 years. Etiology is unknown, immunological mechanisms may play a part because antimitochondrial antibodies are found in almost all patients.

Clinical features

Symptoms
- Asymptomatic: many patients are asymptomatic for years and are discovered on routine examination having hepatomegaly, raised alkaline phosphatase or autoantibodies.
- Pruritus (itching): often preceding jaundice by a few years (This is the earliest symptom) & is produced by accumulation of bile acids.
- Jaundice is present in late stages.
- Diarrhea – resulting from malabosorption of fat sometimes occur (because fat absorption requires bile salts which are not available in the gut due to cholestasis)
- Bone pain or fracture: due to osteomalacia from malabsorption of vitamin D which is fat soluble and requires bile salts for absorption.

Signs

1. Hepatomegaly is almost present while the splenomegaly occurs late when portal hypertension develops.
2. Xanthelasma – yellowish deposition of cholesterol around the eyes & in creases of hand (because cholesterol is not excreted in bile due to cholestasis).
3. Jaundice and signs of portal hypertension are late findings.

Associations

- Primary biliary cirrhosis is associated with other autoimmune disorders such as Sjogren's syndrome, rheumatoid arthritis, keratoconjunctivitis sicca (dry eyes and dry mouth).
- Renal tubular acidosis and membranous glomerulonephritis also occur.

Differential diagnosis

- Chronic biliary obstruction (due to stricture or tumor).
- Carcinoma of bile duct.
- Primary sclerosing cholangitis.
- Sarcoidosis.
- Cholestatic drug toxicity.
- Chronic hepatitis

Investigations

1. LFT: Very high alkaline phosphatase
2. Antimitochondrial antibodies (**AMA**) present in > 95% of cases.
3. Serum cholesterol is high.
4. Serum IgM may be very high.
5. Ultrasound: Diffuse alteration in liver architecture
6. Liver biopsy shows characteristic features such as :
    - Infiltration of portal tract lymphocytes and plasma cells.
    - Loss of small bile ducts.
    - Portal tract fibrosis
    - Granulomas in about 40% cases.

Diagnosis

1. Pruritus
2. Serum alkaline phosphatase very high
3. Antimitochondrial antibodies present
4. No extrahepatic bile duct obstruction on ultrasound.
5. Liver biopsy.

Management

- No specific therapy is available.
- Corticosteroids, azathioprine, penicillamine and cyclosporin have all been tried, but non is effective.
- Ursodeoxycholic acid (Urosofalk) 10-15 mg/kg is of benefit in some patients with improvement in serum liver enzymes and pruritus, and should be given to all patients.

Supportive measures are described as follows:

1. Pruritus

- Cholestyramine :As it is due to bile acid, cholestyramine which is anion-binding resin is given that reduces the bile acids in the body by binding the bile acids in the intestine and increasing their excretion in the stool. Dose: 4-16 g/day orally mixed in orange-juice.
- Rifampicin or ultraviolet light may be helpful in some patients in which cholestyramine is not effective.
- Opioid antagonists such as naloxone and naltrexone may give some benefit.

2. Malabsorption

- Steatorrhea: (fat containing diarrhea) occurs owing to malabsorption of fat. It can be prevented by reducing fat intake to 40 g/d.
- As the fat-soluble vitamins are also not absorbed, monthly injections of vitamin. K (10mg) & vitamin D (Alfacalcidol 1mg/day orally) and calcium supplements should be given.
- Bisphosphonate for osteoporosis.

3 *Hypercholesterolemia* requires statins.

Prognosis

Asymptomatic and those with pruritus usually survive > 20 years. Symptomatic patients with jaundice have rapid course and liver failure occurs in about five years. Liver transplantation is required when bilirubin reaches 100 mic mol/L. Transplantation has a 5- year survival of at least 80%.

SECONDARY BILIARY CIRRHOSIS

This develops after prolonged large bile duct obstruction due to (a) gallstones (b bile duct

stricture. Signs and symptoms are same as that of primary biliary cirrhosis. Diagnosis is based on ultrasound which shows common bile duct dilatation. Cirrhosis, ascites and portal hypertension are late features.

CIRRHOSIS DUE TO HEMOCHROMATOSIS

Hemochromatosis is a condition in which the amount of total body iron is increased that damages the organs including liver. It may be primary or secondary.

PRIMARY HEMOCHROMATOSIS

Primary or idiopathic hemochromatosis is an inhereited autosomal recessive disease characterized by excess iron deposition in various organs in the form of hemosiderin leading to fibrosis and functional organs failure. Liver, pancreas, heart, adrenals, testes, pituitary and kidneys are mostly affected.

- Normal body iron: 3-4 g
- In symptomatic hemochromatosis: 20-40 g
- Iron content is particularly increased in the liver and pancreas (50-100 times normal).

Clinical features

Mostly affecting men aged over 50 years. Menstruation and pregnancy protects women due to iron loss.

1. Patient may come with hepatic cirrhosis diabetes mellitus or cardiomegaly with or without heart failure and conduction disturbances.
2. Bronze pigmentation (leaden-gray skin pigmentation) due to excess melanin and iron occurs in exposed parts, axilla, groins and genitalia.
3. Loss of libido, impotence and testicular atrophy are also common.
4. Arthritis with chondrocalcinosis due to deposition of calcium pyrophosphate.

Investigations

1. Serum ferritin is increased
2. Serum iron concentration increased.
3. Serum iron binding capacity is reduced.
4. Liver biopsy: shows heavy iron deposition and hepatic fibrosis.

Differential Diagnosis

From secondary hemochromatosis which may be due to chronic hemolytic disorders, multiple blood transfusions & dietary iron overload.

Complications

About 15-20% patients with cirrhosis develop hepatocellular carcinoma.

Treatment

- Avoid food rich in iron such as red meat, alcohol, vitamin C, and supplemental iron.
- Venesection of 500 ml (250mg iron) weekly until the serum iron is normal, this may take 2 years or more. When serum ferritin becomes < 50 μg/L maintenance venesection every 2-4 months is performed.
- Chelating agent deferoxamine given as intermittently or continuous infusion may be required if patient does not tolerate vanesection due to anemia or severe cardiac disease.

Course and prognosis

In precirrhotic patients cirrhosis may be prevented with venesection. In patient with cirrhosis, varices may reverse, and risk of variceal bleeding decline with venesection. Liver transplantation leads to survival rate lower than those for other types of liver disease because of cardiac complications.

Screening

Other family members should be screened by checking serum ferritin and iron binding capacity.

SECONDARY HEMOCHROMATOSIS

Secondary causes of iron overload are hemolytic animas such as thalessemia in which multiple transfusions are required. Chelation therapy with deferoxamine is usually required.

CIRRHOSIS DUE TO WILSON'S DISEASE (Hepatolenticular degeneration)

Wilson's disease is an autosomal recessive disorder characterized by copper overload in the body that damages several organs especially liver and brain. The increased copper content is due to increased absorption from small intestine and decreased excretion in bile. The most affected organs are liver, basal ganglia, eyes, kidneys and skeleton.

It is a favorite question in exams especially in contest of cirrhosis in a young patient.

CLINICAL FEATURES

Symptoms usually arise between ages 5 and 30 years. Children usually present with cirrhosis whereas young adults have more neurological problems such as tremor, choreoathetosis, dystonia, parkinsonism and dementia.

It should be considered in any child or young adults with features of chronic liver disease, fulminant hepatic failure or neurologic or psychiatric abnormalities.

Signs.

1. Signs of chronic liver disease, although serum alkaline phosphatase may be low.
2. Neurological signs of basal gangilia involvement such as resting or postural tremor, dystonia of bulbar muscles such as dysarthria and dysphagia.
3. Psychiatric features are behavioral or personality changes and emotional lability.
4. Kayser-Fleischer (Kizer Flisher) ring is pathognomic sign. KF ring is a greenish brown-pigmented ring at the corneoscleral junction just within the cornea, most marked at the superior and inferior poles. KF ring develops due to deposition of copper in the Descement's membrane of cornea. It can frequently be seen with naked eye, however it may require slit-lamp examination. It may be absent in patients with hepatic involvement only but is usually present in those with neuropsychiatric disease.
5. Other associated features: Fanconi defect, renal tubular acidosis, hypoparathyroidism and hemolytic anemia may occur inpatients with Wilson's disease.

INVESTIGATIONS

1. **Serum ceruloplasmin:** Low serum ceruloplasmin (< 20μg/dl) is the best laboratory clue to the diagnosis, although it may be normal occasionally.
2. **24-hours urinary copper.** Urinary copper excretion is increased (>100-1000 μg/24 h). Normal urinary excretion is less than 40 μg/24h.
3. **Serum copper**: Serum copper is reduced (because it is deposited in the tissues), but it may be normal.
4. **Hepatic copper content**: Elevated hepatic copper concentration (> 250 μg/g of dry liver)
5. **Liver biopsy**: Liver biopsy may show acute or chronic hepatitis or cirrhosis.

TREATMENT

Restriction of dietary copper (shellfish, organ foods (Katakat), legumes are rich in copper).

1. **Pencillamine** (Tab. Vistamin 250mg) 0.7-2g/d in divided doses is the drug of choice that chelates and excretes copper through kidney in urine. Pyrodoxine 50mg /week should be added, since pencilamine is an antimetabolite of this vitamin and causes deficiency. The dose can be reduced once the disease is controlled, but treatment must continue for life. Young women should continue to take the drug during pregnancy. Side effects of penicillamine occur in 10% of cases such as skin rashes, leukopenia, and renal damage.
2. **Trientine dihydrochloride:** If patient develops side effects of penicillamine then trientine dihydrochloride 250-500mg three times daily is the next choice.
3. **Zinc acetate:** Oral zinc acetate 50mg 3-times daily promotes fecal excretion of copper and may be used as maintenance therapy after chelation with pencillamine or as a first-line therapy in presymptomatic or pregnant patients.

4. **Ammonium tetrathiomolybdate** is an initial therapy for neurologic Wilson's disease.

5. **Liver transplantation**: indicated for fulminant hepatic failure, end stage liver disease and selected cases of severe neurological disease.

PROGNOSIS

Prognosis is good in patients effectively treated before liver or brain damage has occurred. Neurological damage is permanent.

SCREENING

Family members especially siblings require screening with serum ceruloplasmin, LFTs and slit- lamp examination.

CIRRHOSIS DUE TO ALPHA-1 ANTITRYPSIN DEFICIENCY

This is an autosomal dominant disease in which deficiency of alpha-1 antitrypsin causes liver damage through unknown process.

Some patients present in childhood while some in adult life. About 15-20% of all chronic liver disease in infancy may be attributed to α1- antrypsin deficiency. Cholestatic jaundice in the neonatal period may be the manifestation which can resolve spontaneously. In adults most common manifestation of α1- antrypsin deficiency is asymptomatic cirrhosis and hepatocellular carcinoma, usually over the age of 50 years and about 75% patients will also have emphysema. (occurrence of liver disease is not dependent on the development of lung disease, however these patients should avoid smoking).

Alpha-1 antitrypsin deficiency is one of the differential diagnosis in chronic liver disease (CLD) in young and in patients who have CLD plus emphysema.

Investigations

- **Serum α1- antrypsin:** low
- **Liver biopsy**: Periodic Acid – Schiff (PAS)-positive globules are present seen in periportal hepatocytes.

Treatment

No specific treatment is available other than management of complications of liver disease. Liver transplantation may be advised for advanced liver disease.

JAUNDICE

Jaundice is the yellow discoloration of the sclera, skin and mucus membrane resulting from an increased bilirubin concentration in the body fluid (more than 3mg/dl).

It is very important topic for examination because your patient may have acute or chronic liver disease, congenital hypebilirubinemia, hemolytic anemia or recurrent jaundice.

MECHANISM OF JAUNDICE PRODUCTION

Increase of bilirubin in blood may arise in 4 different ways.

1. **Over production:** Increased bilirubin load on liver cells e.g. hemolytic states.

2. **Decreased hepatic uptake**: Disturbance in process by which bilirubin diffuses into the cells from the sinusoid and is actively transported to the microsome for conjugation (intracellular bilirubin transport).

3. **Decreased hepatic conjugation:** Disturbance of bilirubin conjugation e.g. due to deficiency of enzymes which conjugate it.

4. **Disturbance of excretion:** It may result from intrahepatic dysfunction or extrahepatic mechanical obstruction:
   - Intrahepatic cholestasis: difficulty in canalicular transport of bile from microsome to main bile ducts e.g. viral hepatitis, some drugs.
   - Extra hepatic cholestasis: obstruction of main bile ducts due to common bile duct stone, carcinoma of head of pancrease etc.

TYPES

1. Hemolytic jaundice
2. Congenital hyperbilirubinemia
3. Cholestatic jaundice may be intrahepatic or extrahepatic.

HEMOLYTIC JAUNDICE

This results from increased destruction of red blood cells resulting in increased bilirubin production.

Etiology

1. Extra- erythrocytic abnormalities

- Malaria
- Autoimmune
- Physical trauma (e.g. burns, prosthetic heart valve).
- Chemical trauma (drugs e.g. dapsone)
- Metabolic (e.g. uremia).

2. Intra-erythrocytic defects:

- Spherocytosis
- Thallassemia
- Enzyme Glucose – 6 - phophonate dehydrogenase deficiency
- Vitamin B12 and folic acid deficiency.

Clinical features

- *Jaundice*: mild, because a healthy liver can excrete a bilirubin load 6 times greater than normal. Bilirubin is not more than 4-6 mg/dl in uncomplicated hemolytic anemia. If bilirubin is more than 6 then there is concomitant hepatic injury.
- *Pallor:* due to anemia
- *Splenomegaly*
- *Stool:* dark in color due to excessive stercobilinogen which is produced by bilirubin
- *Urine*: dark due to increased urobilinogen.

Investigations

1. LFT: Plasma unconjugated bilirubin is usually raised but less than 6mg/dl. Liver enzymes and albumin are normal.

2. Urine D/R: No bilirubinemia, because the hyperbilirubinemia is unconjugated which is not water-soluble and therefore cannot pass into the urine. Increased urinary urobilinogen.

3. *Blood:* Low RBC count, high reticulocyte count.

4. *Serum heptoglobulins* are low

CONGENITAL HYPERBILIRUBINAEMIAS

Unconjugated hyperbilirubinemia

- Gilbert's Syndrome (commonest)
- Crigler-Najjar Syndrome

Conjugated hyperbilirubinemia

- Dubin-Johnson Syndrome
- Rotor Syndrome

GILBERT'S SYNDROME

It is the most common congenital hyperbilirubinemia that affects 2-7% of the population. Young adults are mostly affected. Other conditions are rare.

Etiology

The main cause is the partial deficiency of enzyme hepatic glucuronyl transferase that conjugates bilirubin with glucuronic acid, therefore there is impaired conjugation.

Clinical features

It is asymptomatic and usually detected incidental finding of slightly raised bilirubin (1-6 mg/dl) on a routine check. No signs of liver disease are seen. There is a family history of jaundice in 5-15% of patients.

Increase in serum bilirubin after prolonged fasting or calorie deprivation is one of the useful feature for diagnosis in Gilber's syndrome as the patients with hemolysis do not show rise in bilirubin after fasting.

Diagnosis

Low grade unconjugated hyperbilirubinemia, .
No systemic symptoms.
No hemolysis
Normal LFTs.
Liver biopsy (although not necessary) is normal on light microscopy.

Investigations:

Raised unconjugated bilirubin fluctuating from 1.2-3 mg/dl and rarely exceeds 5mg/dl.. LFTs are normal.

Importance of diagnosis

Treatment is not necessary. The importance of establishing this diagnosis is to inform the patient that it is not a serious disease and there is no need for unnecessary investigations in future.

CRIGLER-NAJJAR SYNDROME

There are two types of this syndrome

Type I

Type I is clinically severe form resulting from absent glucuronyl transferase. Infants develop high unconjugated bilirubin levels in serum (20-45mg/dl). Phototherapy may transiently reduce unconjugated bilirubin but there is no benefit of phenobarbitone. Plasmapharesis and liver transplantation are the options. Death occurs usually in first year of life due to kernicterus.

Type II

In type II there is partial deficiency of glucuronyl transferase, unconjugated bilirubin level is not more than 6-20mg/dl. Jaundice present in neonates however it may not appear until adolescence and neurologic complications are uncommon. Phototherapy and phenobarbitone are effective; liver transplantation may require.

CHOLESTATIC JAUNDICE

Cholestasis is a failure of bile flow due to obstruction in intrahepatic or extrahepatic bile ducts.

TYPES

Hepatocellular Jaundice (intrahepatic cholestasis)

It results from inability of liver to transport bilirubin into the bile canaliculii due to swelling of hepatocytes in parenchyma of damaged liver or due to an excretory dysfunction of the bile canaliculi at a cellular level. Hepatocellular jaundice is discussed in the section of acute viral hepatitis.

Obstructive jaundice (Extra-hepatic cholestasis)

It occurs due to large bile duct obstruction of bile flow at any point in the biliary tract distal to the bile canaliculi. Owing to obstruction the bilirubin is unable to enter the bile canaliculi and passes back into the blood, thus, progressively deepening the jaundice.

CAUSES OF CHOLESTATIC JAUNDICE

Intrahepatic

- Viral hepatitis
- Autoimmune hepatitis
- Postoperative jaundice
- Alcoholic hepatitis
- Pregnancy
- Recurrent idiopathic cholestasis
- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Drugs such as oral contraceptives, anabolic steroids.
- Cirrhosis due to any cause.

Extrahepatic

- Common duct stones
- Carcinoma of
  - Head of pancreas
  - Ampulla
  - Bile duct (cholangiocarcinoma)
- Traumatic biliary stricture
- Crystic fibrosis

DRUGS CAUSING HEPATIC CHOLESTASIS

- Sex hormones
- Cyclosporin
- Chlorpromazine
- Haloperidol
- Erythromycin
- Cimitidine/ranitidine
- Nitrofurantoin
- Azathioprine
- Imipramine
- Oral hypoglycemics

BENIGN RECURRENT INTRAHEPATIC CHOLESTASIS

It is characterized by recurrent attacks of pruritus and jaundice, raised serum alkaline phosphatase and morphologic features of cholestasis on liver biopsy. Cholangiography shows no mechanical biliary obstruction. Cirrhosis does not occur, course is benign and remission is the rule.

INTRAHEPATIC CHOLESTASIS OF PREGNANCY

During normal pregnancy, especially in last trimester some derangements in liver function occurs; consisting of slight increase in serum alkaline phosphatase (that is placental in origin). With a normal pregnancy there is no rise of bilirubin or if occurs it is less than 2mg/dl.

In a small number of pregnant women, intrahepatic cholestasis may appear. This usually occurs in third trimester but may develop any time after the seventh week of gestation.
Patient presents with jaundice and pruritus. Serum bilirubin is usually less than 6 mg/dl, serum alkaline phosphatase and cholesterol are elevated significantly.
The clinical features and laboratory abnormalities subside after delivery and are usually normal within 7 – 14 days.

Etiology is unknown but this is suggested that cause is increased sensitivity to hepatic effects of estrogen and progesterone.
The intrahepatic cholestasis is usually termed recurrent jaundice of pregnancy, since the syndrome often (but not always) reappears in subsequent pregnancies.
This disorder shuld be differentiated from viral hepatitis, acute fatty liver of pregnancy and tetracycline induced fatty liver.
Cholestyramine is given for pruritus.

> Causes of recurrent jaundice and chronic liver disease in a young patient are favorite topics of viva.

OBSTRUCTIVE JAUNDICE

Obstructive jaundice most commonly results from stone in common bile duct. Jaundice may be intermittent or persistent and usually associated with right upper quadrant pain, chills and fever. (The combination of jaundice, fever and rigor is called Charcot's triad and it indicates acute cholangitis).

- Jaundice due to obstruction of common bile duct as a result of carcinoma of head of pancreas is usually painless.
- Obstructive jaundice due to stone is not associated with palpable gall bladder while other causes are associated with palpable gall bladder.
- In obstructive jaundice stools are pale (clay-colored), urine is dark and pruritus is present.

Investigations

- Bilirubin is raised, alkaline phosphatase is very high. Occasionally aminotransferases may be elevated.
- Ultrasound and CT scan show dilated bile ducts. MR cholangiography is accurate in demonstrating common duct stone. ERCP is the direct and accurate mean of determining the cause, location, and extent of obstruction.

Clinical features in cholestatic jaundice
Early features
• Jaundice • Dark urine • Pale stool • Pruritus
Late features
• Xanthelasma and xanthomata • Malabsorption • Weight-loss • Steatorrhoea • Osteomalacia • Bleeding tendency

EVALUATION OF JAUNDICE

1. First step is to decide whether the hyperbilirubinemia is due to hemolysis or hepatobiliary disease. This difference can be identified easily by measuring the direct (conjugated) and indirect (unconjugated) bilirubin. In hemolysis there is predominant unconjugated hyperbilirubinemia. There may be features related to hemolytic anemias.
2. If jaundice is due to predominant conjugated bilirubin then decide whether it is the result of hepatocellular disease, intrahepatic biliary obstruction (intrahepatic cholestasis) or extrahepatic biliary obstruction. Diagnosis requires proper history, examination and then investigations.
3. In a long or short case investigations are not available all discussion is based on differential diagnosis in the contest of age, risk factors, incidence and available data from history and clinical examination.

HISTORY

Predisposing factors

Ask about the predisposing factors such as:

- Transfusion, previous surgery, intaravenous drug abuse, promiscuous sexual activity leading to viral hepatitis.
- Alcohol abuse causing alcoholic hepatitis.
- History of medication is important especially the drugs that cause cholestasis such as chlorpromazine or anabolic steroids, drugs that cause hepatocellular damage such as isoniazid or paracetamol.

EXAMINATION

Look for signs of acute and chronic liver disease.

1. Jaundice

- Duration less than 1 month – due to hepatitis.
- Duration 1-2 months – carcinoma or chronic hepatitis.
- Jaundice progressively deepens – obstruction due to malignancy.

2. Fever

- Suggesting viral hepatitis
- Associated rigors suggest cholangitis which occur most often with gallstone causing biliary obstruction.
- Cholangitis presents with (a) Fever (b) Jaundice and (c) Right hypochondrial pain.

3. Pruritus

- Mild to moderate in viral hepatitis
- Intense in obstructive jaundice; due to accumulation of bile salts in the body.

4. Hepatomegaly

Smooth & tender in hepatitis and exrahepatic obstruction and nodular in malignancy.

5. Splenomegaly

Splenomegaly may indicate portal hypertension or chronic liver disease.

6. Signs of chronic liver disease

Clubbing, palmar erythema, anemia, bruises, spider nevi, ascites, gynecomastia, hepatosplenomegaly, and pitting edema.

7. Late features:

In prolonged obstructive jaundice secondary malabsorption develops due to deficiency of bile salts, presenting with:

- Weight loss
- Vit. K deficiency (bleeding)
- Vit D deficiency (bone pain)
- Steatorrhoea

8. Palpable gall bladder

Suggests carcinoma of gall bladder or head of pancreas obstructing the bile duct.

9. Stool

Clay-colored, due to deficiency of bilirubin in obstructive jaundice.

10. Urine:

It is dark in color owing to the renal excretion of conjugated bilirubin.

INVESTIGATIONS

Liver function tests (LFTs)

Serum bilirubin

Slightly increased bilirubin in hemolytic jaundice. Very high in obstructive jaundice and malignancy.

- Unconjugated – in hemolytic jaundice.
- Conjugated – in obstructive jaundice
- Mixed – in hepatocellular jaundice

Liver enzymes:

- High ALT with small rise in alkaline phosphatase indicates hepatitis.
- High alkaline phosphatase with small rise in ALT indicates obstructive jaundice
- No enzymes change indicates hemolytic jaundice.

Serum proteins (albumin)

- Normal in acute hepatitis, hemolytic and obstructive type
- Decreased albumin – in chronic liver disease (e.g. cirrhosis).

Prothrombin time

- Normal – in hemolytic
- Prolonged – in chronic hepatocellular type (e.g. cirrhosis) and in obstructive

Ultrasound

- To detect size of bile ducts, which are dilated in extra- hepatic obstruction (e.g. stone or tumor of common bile duct). It also detects the level of obstruction.
- To demonstrate intra-hepatic lesion.

Urine analysis

- Bilirubin present – cholestatic jaundice (hepatocellular or obstructive).
- Bilirubin absent – Hemolytic
- Urobilinogen increase – Hemolytic

Stool analysis

- Bile pigment absent – in cholestatic jaundice
- Urobilinogen increased – in hemolytic jaundice.

Blood CP

- Leucocytosis – suggests infection (e.g. cholangitis).
- Leucopenia – suggests viral hepatitis.
- Anemia & reticulocytosis – suggest hemolysis

Viral markets

Viral markers for HAV, HEV, HBV, HCV.

Coomb's test for autoimmune hemolysis

Scheme for diagnosis of conjugated hyperbilirubinemia

Liver enzyme normal:

Consider sepsis, Rotor and Dubin- Johnson syndromes.

Liver enzymes elevated:

- If aminotransferases are high, it indicates viral hepatitis, alcoholic hepatitis or sepsis → perform viral markers → ultrasound or CT → liver biopsy.

- If alkaline phosphatase is more high, it indicates intra or extrahepatic obstruction → perform ultrasound → if ducts are dilated biopsy and/or drainage as indicated. If ducts are not dilated then perform ERCP or PTC. If they are abnormal then biopsy of lesion is required, however if the ERCP is normal and LFTs show obstructive pattern; consider cholestatic hepatitis especially drug induced → liver biopsy.

COMMON CAUSES OF JAUNDICE ACCORDING TO AGE GROUP

New born

- Physiological
- Viral
- Rh incompatibility
- Biliary atresia

Young person

- Thallassemia, sickle cell anemia or spherocytosis
- Gilbert's syndrome (congenital hyperbilinubinemia)
- Viral hepatitis
- Drugs: e.g. chlorpromazine, anti-depressant, anti-tuberculosis.

Middle aged person

- Hemolytic anemia
- Viral hepatitis
- Alcoholic hepatitis
- Drug induced hepatitis
- cirrhosis of liver
- Gall-stone obstruction

Elderly person

- Primary or secondary carcinoma
- Hemolytic anemia
- Cirrhosis of liver
- Drug induced hepatitis
- Gall stone & carcinoma pancreas.

CAUSES OF HEPATOMEGALY

Infections

viral

- Hepatitis
- Infectious mononucleosis

Bacterial

- Pyogenic liver abscess
- Typhoid
- Brucellosis syphilis of liver

Parasitic

- Malaria
- Kalazar
- Schistosomiasis
- Hydatid cysts

Early cirrhosis
Alcoholic fatty liver

Congestive

- Congestive cardiac failure
- Constrictive pericarditis
- Budd- Chiari syndrome (obstruction of hepatic vein)

Neoplasm

- Hepatocellular carcinoma
- Cholangiocarcinoma
- Secondary tumors (metastatic)
- Leukemias
- Lymphoma
- Myeloproliferative disorders

Apparent

- Low-lying diaphragm as in emphysema
- Reidel's lobe of liver (projection in right iliac fossa)

Common causes of hepatomegaly

- Hepatitis
- Cirrhosis
- Liver abscess
- Congestive
- Neoplastic
- Hydatid cyst

Causes of painful hepatomegaly

- Viral hepatitis
- Liver abscess
- Congestive cardiac failure
- Hepatocellular carcinoma

Causes of hepatosplenomegaly

- Chronic liver disease
- Myeloproliferative diseases
- Lymphoproliferative disorders such as chronic lymphocytic leukemia, lymphoma.
- Disseminated tuberculosis
- Brucellosis, Infectious mononucleosis
- Megaloblastic anemia
- Chronic hemolytic anemia
- Gaucher's disease
- Amyloidosis
- Congestive cardiac failure

CAUSES OF SPLENOMEGALY

Massive
More than 8 cm below the costal margin or reaching to the umbilicus.

- Chronic malaria, kalazar
- Chronic myeloid leukemia (CML)
- Myelofibrosis
- Primary lymphoma of spleen
- Rarely in portal hypertension also

Moderate
About 4-8 cm below costal margin orlarge but not reaching to umbilicus.

- All causes of massive splenomegaly (obviously it is moderate before massive)
- Portal hypertension
- Leukemia, lymphoma
- Thallasemia
- Gaucher's disease

Small
Just palpable or 2-4 cm

- The causes listed above
- Polycythemia, hemolytic anemia
- Malaria, infective endocarditis, hepatitis, infectious mononucleosis.
- SLE, RA, polyarteritis nodosa

LIVER TRANSPLANTATION

Liver transplantation is the replacement of native diseased liver by a normal organ (allograft) recovered from a brain- dead donor.

Liver transplantation should be considered for acute or chronic liver disease that is progressive, life- threatening and unresponsive to medical therapy. End –stage liver disease in which patient is experiencing life – threatening complications of hepatic decompensation, whose quality of life has deteriorated to unacceptable levels. Although disease should be advanced yet the procedure should be done sufficiently early to give surgical procedure a fair chance of success.

Indications

- Fulminant hepatic failure due to any cause
- Chronic hepatitis with cirrhosis
- Chronic viral hepatitis B, C
- Primary and secondary biliary cirrhosis
- Autoimmune hepatitis
- Alcoholic liver disease
- Wilson's disease
- Alpha-1 antitrypsin deficiency
- Sclerosing cholangitis
- Hepatic vein thrombosis
- Primary hepatocellular carcinoma < 3 small lesions (< 3cm) or a solitary nodule of < 5cm
- Hepatic adenomas

Contraindications

- Sepsis outside the hepatobiliary tree
- Advanced cardiac or pulmonary disease
- Active drugs or alcoholic abuse
- Liver metastasis
- HIV infection
- Hepatocellular carcinoma – because recurrence rate is high
- Age above 65 years.
- High replicative hepatitis B.
- Uncontrolled psychiatric illness.

Donor selection

The donors are usually victims of head trauma with brain death. Donor should be ABO compatible and hemodynamically stable with normal renal, hepatic and pulmonary function, he should be infection- free. There is no need for tissue matching for HLA- matching.

Procedure

Following perfusion with cold electrolyte solution, the donor liver is removed and packed in ice, its preservation time can be up to 20 hours. The recipient operation takes about 8 hours. Portal hypertension, thrombocytopenia and coagulopathy leads to a large amount of blood loss when native liver is removed; requiring large blood products transfusion during surgery. Very intensive post- operative care is required to prevent complications (e.g. infections and hemodynamically instability)

Rejection

Acute or cellular rejection is usually seen 5-10 days post- transplant; it can be asymptomatic but often there is a fever, histologically there is portal infiltrate with prominent eosinphils, bile duct damage and endothilatis of blood vessels. This type of rejection responds to immunosuppressive therapy (e.g cyclosporin).

Chronic rejection is seen from 6 weeks to 9 months post- transplant, with disappearance of bile ducts, narrowing and occlusion of arteries. This type of rejection may rarely be reversed by immunosuppressive therapy and often requires retransplantation.

IMPORTANT HEPATOTOXIC DRUGS

- Paracetamol
- Halothane
- Phenothiazine e.g. chlorpromazine
- Antituberculous drugs e.g. isoniazid, rifampicin and pyrazinamide
- Methyldopa
- Erythromycin, sulphonamide

LIVER ABSCESS

Types

1. Amoebic liver abscess
2. Pyogenic liver abscess

AMOEBIC LIVER ABSCESS

This type of liver abscess is caused by Entamoehba histocytica carried from the bowel to the liver in the portal venous system. Portal inflammation results with the development of multiple microabscess and eventually single or multiple large abscesses.

This disease is more common in adult male. History of amoebic dysentery may or may not be present.

CLINICAL FEATURES

The onset is usually gradual but it may be sudden presenting as acute abdomen with fever, right hypochondrial pain and tender hepatomegaly. However about 50% patients have no symptoms related to liver involvement and they present with fever of unknown origin, especially elderly.

History

Pain or discomfort in liver area

- Pain is initially dull and aching or sensation of heaviness in right hypochondrium, later it becomes sharp and stabbing.
- Pain is referred to the tip of right or left shoulder when abscess is located high in right or left lobes of the liver.
- Pain may be increased by deep inspiration or coughing & decreased when patient tends to lean the left side.

Constitutional symptoms

- Fever: initially high, later remittent or intermittent. Rigors may occur.
- Anorexia, malaise and weight loss.

On examination

- Patient is ill-looking, toxic and febrile.
- *Enlarged tender liver*: Localized visible bulge may be seen in epigastrium or right hypochondrium. Liver is palpable and is severely tender.
- *Local edema* of chest or abdominal wall may be present.
- *Compression test:* Pain on firm pressure with fingertips on intercostal space over a limited area is a common and valuable in localizing the abscess. Punch test may be performed that produces tenderness in specific area of right hypochondrium.
- Jaundice is usually absent.

COMPLICATIONS

1. Extension to the lung through diaphragm causes basal pneumonia of right side.
2. Sterile pleural effusion of right side: it usually resolves with medical therapy.
3. Rupture into the pleural space: it requires drainage with chest tube.
4. Hepathobronchial fistula may cause cough productive of large amounts of necrotic material that may contain amebas. This dramatic complication carries good prognosis.
5. Rupture into the peritoneum: presents as acute abdomen and requires surgical intervention.
6. Rupture into the pericardium: usually due to the abscess of left lobe of liver and requires surgical intervention.

INVESTIGATIONS

1. **Blood CP:**
   Leucocytosis with predominance of neutrophils.
2. **Stool D/R:**
   Ameba may be present or absent.
3. **X-ray chest**: Right side of diaphragm is raised, there may be right sided consolidation or pleural effusion.
4. **Ultrasound:** Ultrasound is useful for detecting abscess and is the investigation of first choice.

- Amebic liver abscess is usually single and in right lobe.
- In majority of patients who have symptoms more than 10 days have single abscess in the right lobe of liver; however in initial 10 days

abscess may be multiple that coalesce and develop single abscess later.

- Multiple abscess should be differentiated from pyogenic abscess, because pyogenic abscesses are usually multiple.
- Complete resolution of abscess on ultrasound takes 6 months to one year, therefore frequent follow up ultrasounds are not advised.

5. **CT scan or MRI** may be required in some patients in whom diagnosis on ultrasound is doubtful.
6. **Serological test for ameba:** Indirect hemagglutination test for detection of antibodies against Entameba histolytica is positive in 95% of patients.
7. **Diagnostic aspiration of fluid:** Aspirated fluid is sent for Gram staining, culture and detection of ameba. Ameba may be present in 50% patients who are acutely toxic.

TREATMENT

1. Metronidazole (Flagyl) 800mg 8-hourly orally for 10 days. If patient has nausea and vomiting then start with injection Flagyl 500mg 8-hourly and switch over to oral when patient can tolerate. About 90% patient respond dramatically to metronidazole within 72 hours with reduced pain and fever.
2. Diloxanide furoate (Tab. Entamizole DS 500mg) 3-times daily for 10 days to eliminate intestinal infection.
3. Aspiration of liver abscess

Indications of aspiration

- Failure to respond clinically in 3-5 days.
- The threat of imminent rupture
- The need to rule out pyogenic abscess, particularly in patients with multiple lesions.
- Left-lobe abscess: to prevent rupture into the pericardium.
- Large abscess (> 10cm).

Procedure: A wide bore needle is inserted into the area of maximum tenderness or into 8^{th} or 9^{th} intercostals space in midaxillary line. All available fluid should be removed. Ultrasound guided procedure may be performed.

PYOGENIC LIVER ABSCESS

Patients with pyogenic liver abscess are usually older and have some predisposing factors as following:

1. Ascending cholangitis: resulting from biliary obstruction due to stone, stricture or neoplasm is the most common predisposing factor for liver abscess.
2. Portal pyemia: from intra-abdominal sepsis e.g. appendicitis or perforations.
3. Abdominal trauma.

Organism

1. E. Coli (most common)
2. Streptococcus fecalis
3. Proteus vulgaris
4. Anaerobes such as bacteroides
5. Staphylococcus aureus (occasionally).

CLINICAL FEATURES

Clinical features are similar to amebic liver abscess. Onset is often insidious but may be acute.

Insidious onset

- Fever is almost always present.
- Pain and tenderness in right hypochondrium or epigastrium.
- Rigors, anorexia, vomiting, weight loss.

Acute onset

- Tender hepatomegaly.
- Signs of pleural effusion or pleural rub in the right lower chest.
- Gram negative septicemia with shock can occur.

INVESTIGATIONS

1. Blood CP

- Leucocytosis
- Normocytic normochromic anemia.

2. LFTs

- Serum bilirubin is raised in 50% of cases.
- Serum alkaline phosphatase is raised in 90% of cases.
- Serum ALT is elevated in 48% of cases.

4. **Serum B_{12}** --- very high (as vitamin B12 is stored and subsequently released from the liver).
5. **Blood culture**: Positive only in 30% cases.
6. **X-ray chest** – Raised right diaphragm if the abscess is in right lobe.
7. **Ultrasound** is useful but CT or MRI may be required.

TREATMENT

Combination therapy

- Third generation cephalosporin such as cefotaxime (Inj. Claforan) 1g 8-hourly plus
- Metronidazole (Inj. Flagyl 500mg) 8-hourly; to cover anaerobes.

If cost is the problem then use triple regime:

- Ampicillin (Inj. Penbritin 500mg) 1g 6-hourly
- Gentamicin (Inj. Gentacin) 80 mg 8 hourly
- Metronidazole (Inj. Flagyl) 500mg – 8 hourly.

Aspiration of liver abscess

Aspiration should be performed if the size of abscess is at least 5cm or response to antibiotic is not rapid; catherter or laproscopic drainage should be undertaken.

PROGNOSIS

Mortality rate is about 10-25%. Scattered multiple abscesses have very high mortality.

Differences between amebic and pyogenic liver abscess

Factors	Amebic	And Pyogenic
Age	Any age	Usually older
Number	Usually single	Usually Multiple
Predisposing factors	Usually absent	Mostly present
Jaundice	Unusual	May be present
Organisms	E.histolytica	E. coli, Anaerobes
Aspiration	Usually not required	Usually required
Treatment	Metronidazole	Third generation and metronidazole

HEPATOCELLULAR CARCINOMA (HEPATOMA)

ETIOLOGY

1. Chronic hepatitis C virus infection
2. Chronic hepatitis B virus infection
3. Alcoholic cirrhosis and cirrhosis due to hemochromatosis.
4. Cirrhosis is present in 80% of cases and may be of any type, however risk is low in primary biliary cirrhosis and Wilson's disease.
5. Ingestion of aflatoxin-contaminated foods. (aflatoxin is a metabolite of a fungus found in ground-nut).
6. Androgens, anabolic steroids & contraceptive pills.

CLINICAL FEATURES

- Hepatoma usually presents usually below the age of 50 years. Male to female ratio is 4:1.
- It may be single or as multiple nodules throughout the liver.

Symptoms

1. Weight loss, weakness, anorexia and fever.
2. An ache or discomfort in the right hypochondrium and ascites. (The rapid development of these features in a cirrhotic patient is suggestive of hepatoma).
3. Paraneoplastic syndrome in small number of patients presenting as:
   - Increased hematocrit due to erythocytosis as a result of erythropoietin-like activity of the tumor.
   - Hypercalcemia due to secretion of parathyroid-like hormone.
   - Hypoglycemia, hypercholesterolemia and dysfibrinogenemia.

On examination

1. Enlarged, irregular, tender liver may by palpable.
2. Hepatocellular carcinoma is vascular and bruit may be heard over the liver.
3. Blood-tinged ascites-in 20% of cases.

Metastasis

Metastasis mainly occurs in regional lymph nodes, lungs and bones. Tumor also spreads into inferior vena cava and portal vein.

INVESTIGATIONS

1. **Alpha-fetoprotein** is raised (> 500μg/L) in 70-80% of cases. Mild elevations may occur in acute or chronic hepatitis and metastasis from gastric or colonic tumors.
2. **LFTs**: Serum alkaline phosphatase is raised.
3. **Imaging:** Ultrasound is the first imaging tool, it can detect tumor larger than 3 cm. MRI is being used with increasing frequency.
4. **Liver biopsy** – Diagnosis can be confirmed on ultrasound or CT scan guided biopsy.

TREATMENT

Surgery

Surgical removal requires a tumor confined to one lobe in the absence of cirrhosis, however resection is occasionally possible because of underlying cirrhosis, involvement of both hepatic lobes, or distant metastasis (common sites are lung, brain, bone, and adrenal.

Palliative therapy

- Chemotherapy has not been shown to prolong life, but hepatic artery embolization with chemotherapy (chemoembolization) may be palliative.
- Injection of small tumor (< 3cm) with alcohol may prolong life and give palliation.
- Radiotherapy is unhelpful.
- Liver capsule expansion causes severe pain requiring opioids. Pain relief has prime importance.

Liver transplantation

Liver transplantation in small tumor (one tumor < 5cm or three or less than three tumors each < 3cm in diameter) proves 5-years survival in about 75% of cases.

PROGNOSIS

Survival is less than 6 months after diagnosis.

SCREENING

Patients of cirrhosis should be screened for hepatocellular carcinoma every 6 months with serum alpha-fetoprotein and ultrasonography. The risk of hepatocellular carcinoma in a patient with cirrhosis is 3-5% per years.

BUDD-CHIARI SYNDROME

Budd-Chiari syndrome is characterized by occlusion of hepatic vein leading to obstruction to the venous outflow of liver, in 1/3 of patients cause is unknown. It is a common MCQ.

Etiology

1. Hypercoagulability states:
   - Polycythemia vera
   - Oral contraceptives
   - Leukemia
2. Hepatocellular carcinoma
3. Posterior wall sarcoma
4. Renal or adrenal tumors
5. Hepatic infection such as hydatid cyst
6. Radiotherapy
7. Trauma to liver

Clinical features

Acute presentation: abdominal pain, nausea, vomiting, tender hepatomegaly and ascites.

Chronic presentation: hepatomegaly (particularly enlargement of caudate lobe), mild jaundice, ascites and splenomegaly with portal hypertension.

Investigations

- *Ascitic fluid analysis* shows high protein content.
- *Liver biopsy* shows congestion, fibrosis and cirrhosis.
- *Ultrasound, CT or MRI* shows hepatic vein occlusion with diffuse abnormal parenchyma with prominent caudate lobe; since its drainage may not be occluded.
- *Color Doppler ultrasound* to detect venous occlusion is the investigation of choice.

Differential diagnosis

- Inferior vena caval obstruction
- Right heart failure
- Constrictive pericarditis

Treatment

- Ascites: salt and water restriction and diuretics.
- Treatment of underlying cause.
- Portocal shunt or TIPS procedure may be reqiored to relieve hepatic congestion. Ballon angioplasty with stenting may be performed if there is short segment of thrombosis in the hepatic vein.
- Liver transplantaion should be considered in patients with cirrhosis and hepatic dysfunction.
- Life- long anticoagulation often required.

GALLSTONES

TYPES OF GALLSTONES

1. Cholesterol stones:

- Pure cholesterol stone (10%)
- Mixed stone (90%) composed of cholesterol, bile pigments and calcium.

2. Pigment stones

RISK FACTORS

Cholesterol stones

The excessive secretion of cholesterol by liver is the most important factor in stone formation. Increased cholesterol secretion occurs in the following conditions:

- Females (male to female ratio 1:3)
- Obesity
- Exogenous estrogen
- Increased age (mostly 40 onwards) rare in young).
- Diabetes mellitus (associated with high cholesterol)
- Pregnancy
- Rapid weight loss

Pigment stone

- Hemolytic anemias
- Ileal disease or resection
- Infection of biliary tract
- Bile stasis

PATHOGENESIS

Cholesterol stones

These stones develop when bile is supersaturated with cholesterol relative to bile salts i.e. cholesterol secretion is increased or bile salts are reduced. Decreased amount of bile salts may be due to defective synthesis or excessive intestinal loss.

Cholesterol is insoluble, bile salts and phospholipids make it soluble in gallbladder and prevents from precipitation. If cholesterol is reduced, precipitation of cholesterol occurs, forming gallstones.

Pigment stones

Like cholesterol unconjugated bilirubin is insoluble and precipitates in gall bladder. Conjugation of bilirubin prevents this precipitation. When unconjugated bilirubin level is high in conditions such as hemolytic anemia or infection in the biliary tree causing deconjugation of bilirubin via bacterial beta-glucuronidase, bilirubin precipitates forming gallstones.

CLINICAL FEATURES

1. **Asymptomatic:** about 80% of cases are asymptomatic.
2. **Symptomatic gallstones** manifest either as biliary colic or cholecystitis.
3. **Biliary colic** occurs if the stone is acutely impacted in the cystic duct. Pain is felt in the epigastrium (in 70% cases) or right upper quadrant (in 20% cases), radiating to the interscapular region or tip of the right scapula.

COMPLICATIONS

1. Acute and chronic cholecystitis
2. Gallstones may pass into common bile duct, giving rise to biliary obstruction that produces pain in right upper quadrant with or without obstructive jaundice.
3. Rarely gallstone may perforate through the wall of an inflamed gall bladder into the

intestine, producing a fistula and if stone is large it impacts in terminal ileum causing intestinal obstruction.

4. Mucocele or empyema of gallbladder: completely obstruction of cystic duct leads to slow distention of the gallbladder from continuous secretion of mucus, forming mucocele. If this material becomes infected empyema develops.

INVESTIGATIONS

Ultrasound

- It is the method of choice for diagnosis of gall stone.
- It shows dilated extra-and intra hepatic ducts when common bile duct is obstructed.

Endoscopic retrograde cholangiography (ERCP)

It determines the cause of common bile duct obstruction. Stones can be removed from common bile duct during the procedure.

X-Ray abdomen

Plain x- ray abdomen shows gallstones in 10-20% of cases only. Therefore this is not useful investigation for diagnosis of gallstone.

MANAGEMENT

Asymptomatic – no treatment.
Symptomatic—following are the options

Surgery (cholecystectomy)

Laproscopic (preferred) or open surgery is the treatment of choice for symptomatic gallstones. This procedure is suitable for most of the patients, including those with acute cholecystitis (even in pregnancy).

Endoscopic sphincterotomy

Common bile duct stones can be removed by endoscopic technique.

Gallstone dissolution

Cholesterol stones can be dissolved by bile acids chenodeoxycholic acid and ursodeoxycholic acid, which increase cholesterol solubility in bile; they only dissolve radiolucent stones. Only 10% patients are suitable for this therapy especially those who refuse surgery Suitable patients are those with functioning gallbladder (visualized by oral cholecystography), multiple small floating gallstones. Gallstones dissolution takes 6 months- 2 years. Stone recur in 50% of patients after treatment is stopped.

Lithotripsy

Shock wave treatment of gallstones (lithotripsy) can be carried out using ultrasound- guided lithotripters for single radiolucent stones less than 20 mm in diameter with advantage of being non – invasive and safe, but usually not recommended.

Treatment of gall stone
- Cholecystectomy open or laproscopic
- Bile acids—chenodeoxycholic acid or ursodeoxycholic acid.
- Dissolution
- Lithotripsy
- Endoscopic sphincterotomy.

CARCINOMA OF GALLBLADDER

- Age: 65-70 years.
- Sex: Mostly females (male to female ratio 1:4) squamous cell carcinoma 10%.
- Etiology: gallstones, cholecystitis. (Although cancer occurs only in 1% cases of gallstone).

CLINICAL FEATURES

1. Abdominal pain: Right upper quadrant pain radiating to back.
2. anorexia, weight loss
3. Jaundice: obstructive jaundice secondary to local spread of the tumor to the common bile duct.
4. Courvoisier's law: A palpable gallbladder with obstructive jaundice is said to signify malignant disease.
5. Hepatomegaly with liver tenderness.

INVESTIGATIONS

1. Ultrasound
2. X-ray may show gallbladder calcification
3. LFTs show: features of obstructive jaundice. (high conjugated bilirubin and alkaline phosphates)

TREATMENT

The treatment is surgical excision but the cancer has frequently extended beyond the walls of the gallbladder into the liver and surrounding tissues (metastasis), therefore, unresectable. Prognosis is poor.

CHOLANGIOCARCINOMA

Carcinoma of the bile duct (cholangiocarcinoma) affects both sexes equally in a patient aged 50-70 years. Two third tumors arise from intrahepatic bile ducts while the one third from extrahepatic bile ducts. There is an increased incidence in patients with ulcerative colitis especially those with sclerosing cholangitis.

Clinical features are progressive jaundice, right hypochodrial pain, fever and chills (due to choalngitis).

Investigations show conjugated hyperbilirubinemia, raised alkaline phosphatase and normal AST. Elevated tumor marker CA 19-9. Ultrasound and CT show biliary dilatation and mass. MRI and MRCP permits visualization of biliary tree.

Treatment: surgery is suitable in less than 10% of cases, palliative measures such as insertion of metallic stents thorough endoscope. Radiotherapy may relieve pain and contribute to biliary decopression. Cholangiocarcinoma is generally considered contraindication for liver transplantation due to rapid tumor recurrence, except in very early stage.

COMMONLY USED DRUGS IN HEPATOBILIARY DISEASES

Following are the commonly used brands of drugs. Pharmaceutical companies are invited for advertisement of their products.

T: tablet; C: capsule, I: injection, S: syrup

HEPATITIS a VACCINE
Inj. Harvix 0.5ml, 1ml (GlaxoSmithKline)
Over 16 years age 1ml IM in deltoid 0, 2-4 weeks, then 6-12 months.

HEPATITIS B VACCINE
Inj. Engerix – B 10, 20 mcg (GlaxoSmithKline)
Above 10 years 20mcg IM in deltoid at 0, 1, 6 months.

INTERFERON ALPHA 2a
Inj. Roferon – A (Roche) 3, 4.5, 9, 18 mega units

INTERFERON ALPHA 2b
Inj. Uniferon 3, 5 million units (Getz Pharma)
Inj. Heberon alpha – 2b 3million units (Macter)

HEPATITIS B IMMUNOGLOBULIN
Inj. Bayhep B 217 IU (1ml) Bayer
Dose:0.06ml/kg IM as soon after exposure as possible (preferably within 7 days). Injection is available in 1ml (217 IU) and 0.5ml

LACTULOSE
Syp. Duphalac

Penicillamine
T. Vistamin 250 mg

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- **Ultrasound:** upper abdomen, pelvis, whole abdomen. Ultrasound guided biopsy.
- **Endoscopy**: upper and lower GI endoscopy, sclerotherapy, banding.
- **CT scan**: abdomen, CT guided biopsy
- Liver biopsy
- Peritoneal biopsy
- X- ray abdomen
- **Surgical procedures** especially TIPS surgery.
- **Oncologists**: peoples have very little information about good oncologists and hematologist, please inform about good oncologists.

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RESPIRATORY DISEASES 4

EXAMINATION OF RESPIRATORY SYSTEM

Introduction
Introduce yourself to the patient and get permission for examination (e.g. I am Dr. Inam Danish and I would like to examine you). In our system if you ask someone " can I examine you?" the response may be "no" as the patient might be irritated due to practice of large number of students on him before viva exam.

Position of patient
Patient should be lying in a semirecumbent position on a bed with arms sufficiently abducted to allow access to the axillary region.

Exposure
Expose the male patient fully from chest and abdomen up to the umbilicus. Female patient should not be exposed by a male doctor.

Scheme of examination
During viva common command is "examine the respiratory system" start examination from inspection, then palpation, percussion and auscultation should be performed. It is important to remember that general physical examination related to repiratory system should always be performed at the end. You may face questions related to clubbing, cyanosis and lymphadenopathy. These system related findings of general physical examination are very helpful in diagnosis. This rule also applies for other systems.

EXAMINATION OF CHEST

- First examine the front and side of the chest with the patient lying in semirecumbent position on a bed with the arms sufficiently abducted to allow access to the axillary region.
- Then examine the posterior aspect of chest with the patient sitting upright with arms folded across the chest.
- Complete the examination anteriorly with inspection, palpation, percussion and auscultation, then change the position of patient and examine posterior of chest with the similar pattern as adopted in examination of front e.g inspection, palpation, percussion and auscultation.

INSPECTION

It should be performed from the foot end of the bed. Inspection of chest can be completed under three headings: A, B, C.

A: Appearance

It includes shape and symmetry of chest and lesions of the chest wall.

Shape and symmetry of the chest

Barrel chest
When the anteroposterior (AP) diameter is increased compared with the lateral diameter, the chest is described as barrel-shaped. The increased AP diameter indicates hyperinflation and is seen in patients with severe asthma or emphysema.

Pigeon chest (pectus carinatum)
A pigeon chest is a localized prominence (an outward bowing of the sternum and costal cartilage). Pectus carinatum develops in rickets and in chronic childhood respiratory illness in which it results from repeated strong contractions of diaphragm while the thorax is still pliable.

Funnel chest (pectus excavatum)
It is a developmental defect involving a localized depression of the lower end of the sternum. In severe cases lung capacity may be restricted.

Harrison sulcus
It is a linear depression of the lower ribs just above the costal margins at the site of attachment of diaphragm. It can result from severe asthma in childhood or rickets.

Kyphosis
Kyphosis refers to exaggerated forward curvature of spine, while scoliosis is lateral bowing. Kyphoscoliosis, a combination of both shapes may be idiopathic or secondary to poliomyelitis or Marfan syndrome. Severe kyphoscoliosis may reduce the lung capacity and increase the work of breathing.

Lesions of the chest wall

Look for the scars of previous thoracic surgery, chest tube insertion due to pneumothorax or pleural effusion. Prominent veins may be seen in patient with superior vena caval obstruction.

B. Breathing

Respiratory frequency
Normal resting respiratory rate is about 14 breaths/min. It increases in fever, respiratory infections, asthma, COPD, and pulmonary edema.

Mode of breathing

- Men usually have abdominothoracic type of respiration in which abdomen moves outwards during inspiration due to downward movement of diaphragm,. This normal pattern can be reversed (i.e. thoracoabdominal) when there is peritonitis, or raised intra-abdominal pressure due to ascites or gaseous distension of bowel.
- Women usually have thoracoabdominal type of respiration with the use of intercostals muscles and therefore respiratory movements are predominantly thoracic. This normal pattern can be reversed in pleuritis, paralysis of intercostal muscles and ankylosing spondylitis.

C: Chest movements

- Look for the asymmetry of chest wall movement.
- Unilaterally diminished movement indicates underlying local lung disease such as consolidation, collapse, pleural effusion and pneumothorax.
- Bilateral reduction of chest wall movement indicates a diffuse abnormality such as COPD or diffuse pulmonary fibrosis.

PALPATION

Apex beat

- Displacement of apex beat to the side of lesion may result from collapse of the lower lobe or by localized pulmonary fibrosis.
- Displacement of apex beat away from the side of lung lesion can be caused by pleural effusion or tension pneumothorax.
- Apex beat is often impalpable in overinflated lung due to COPD.

Trachea
The forefinger of right hand is pushed up and backwards from the suprasternal notch until the trachea is felt. If the trachea is displaced to one side its edge rather than its middle will be felt and a larger space will be present on one side than other. Significant displacement of trachea suggests disease of the upper lobe of lung. Sometimes trachea is displaced due to mediastinal mass such as lymphoma and carcinoma.

- Tracheal displacement to the side of lung lesion: upper lobe collapse or fibrosis.

- Tracheal displacement away from the side of lung lesion: massive pleural effusion, tension pneumothorax.

Tracheal tug: when the fingers are placed on trachea above the suprasternal notch and is felt that trachea moves inferiorly with each inspiration, this is called tracheal tug. It is a sign of gross overinflation of chest because of airflow obstruction such as in COPD.

Chest movements
Place the hand firmly on the chest wall with the fingers extending around the sides of the chest. The thumbs should almost meet in the midline and should be lifted slightly off the chest so that they are free to move with respiration. As the patient takes a deep breath in, the thumbs should move symmetrically apart on both sides. Reduced chest movement on one side indicates a lesion on that side e.g pleural effusion, consolidation, collapse, pneumothorax and localized fibrosis.

Chest expansion

Examine chest expansion with measuring tape keeping it below the nipple. Chest expansion during inspiration more than 5cm as compared to expiration is considered normal and less than 2cm or less as definitely abnormal. Reduced chest expansion indicates generalized process involving the lungs that restricts their expansion such as bronchial asthma, emphysema, pulmonary fibrosis. Conditions which restrict movement of ribs such as ankylosing spondylitis also reduce expansion.

Tactile Vocal Fremitus (TVF)

Vocal fremitus is the transmission of voice sounds to the chest wall and palpable as low frequency vibration. Palpate the chest wall with the palm of the hand while the patient repeats "ninetynine" or teen, teen, teen in Urdu. Compare the both sides. TVF increases in consolidated area and decreases due to pleural effusion and pleural thickening.

PERCUSSION

The positions in which the percussion note on the two sides should be compared are as follows:

Anterior chest wall

- Calvicle
- Infraclavicular region
- Second to sixth intercostals spaces

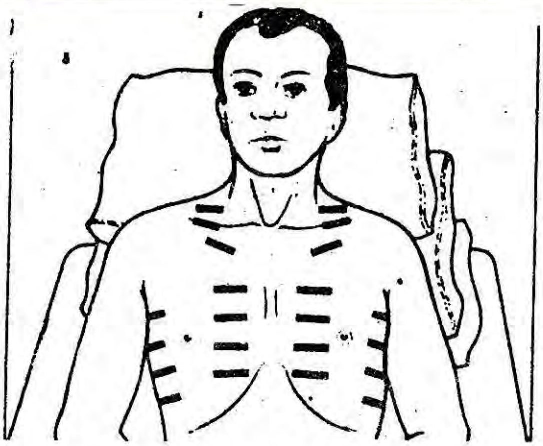
Lateral chest wall

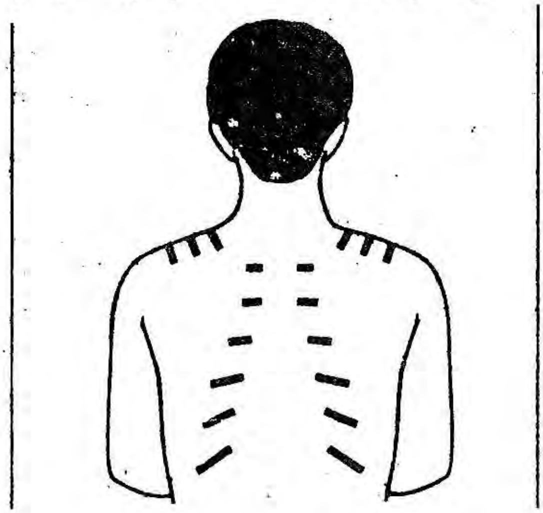
Fourth to seventh intercostal spaces.

Posterior chest wall

- Percuss at trapezius and percussing downwards over the lung apex.
- Above the level of spine of scapula
- At intervals of 4-5 cm starting from below the level of spine of scapula down to the eleventh rib.

PERCUSSION NOTE	
Character	**Causes**
Hyper-resonant	Due to hyperinflation as in emphysema, asthma pneumothorax Very thin people
Dull	Consolidation, collapse, fibrosis, obesity
Stony dull	Pleural effusion





AUSCULTATION

Object

Object of auscultation is to listen for:
Quality of breath sounds.
Intensity of breath sounds
Presence of added sounds.

Areas of auscultation

Ant: from above the clavicle down to the sixth rib.
Lat: from axilla to the eight rib
Post: down to the level of the eleventh rib.

How the breath sounds are produced

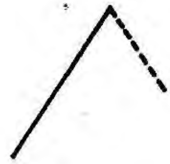
Breath sounds are produced by vibration of the vocal cords caused by turbulent flow of air through the larynx during the breathing. The sounds so produced are transmitted along the trachea and bronchi and through the lungs to the chest wall. In their passage normal lungs the intensity and frequency pattern of sounds is decreased since normal alveoli act like silencer and transmit sounds poorly. When they are heard through a stethoscope on the chest wall they have a characteristic rustling quality to which term ***vesicular breathing*** is applied. The sound is similar to the sound of wind rustling in the leaves. The intensity of sound increases steadily during inspiration and then quickly fades away during the first one-third of expiration.

When the normal function of alveoli is lost, as they become solid, instead of spongy in consolidation, their silencing effect is lost and the sounds produced in bronchi are transmitted to the chest wall without filtered by alveoli, this is called *bronchial breathing*. It must be noted that absence of bronchial breathing does not rule out consolidation.

Quality of breath sounds

Normal vesicular breathing

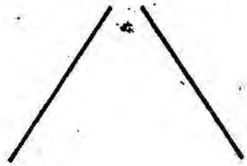
- Louder and longer on inspiration than on expiration.
- Expiration is shorter and softer than inspiration.
- There is no gap between inspiration and expiration.



Vesicular
Rustling quality Expiration shorter and softer than inspiration and continuous with it

Bronchial breathing

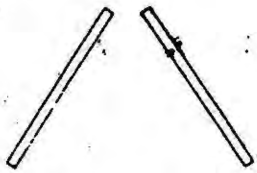
- Inspiration and expiration are of same duration and intensity.
- There is gap between inspiration and expiration.
- Vocal resonance is increased to allow whispering pectoriloquy to be heard.



Bronchial
Loud and clear. Expiration and inspiraton of same duration and intensity

Amphoric or cavernous breathing

It is an exaggerated bronchial breathing and heard over a large cavity.



Cavernous
As for bronchial, but more 'hollow' in quality

CAUSES OF BRONCHIAL BREATHING
Common
Lung consolidation
Uncommon
• Localized pulmonary fibrosis
• Above the pleural effusion
• Collapsed lung with patent bronchus

Intensity of breath sounds

Intensity of breath sounds may be normal or reduced. Causes of decreased breath sounds are:

Bilateral

- Emphysema
- Thick chest wall

Unilateral

- Pleural effusion
- Pneumothorax
- Pneumonia
- Large neoplasm
- Pulmonary collapse

Added sounds

Wheezes or rhonchi

These are musical or whistling sounds produced by the passage of air through narrowed airways e.g. as in asthma. Rhonchi should be timed in relation to the respiratory cycle. They may be heard in expiration or inspiration or both, however inspiratory rhonchi indicate severe airway narrowing.

In asthma rhonchi are mainly expiratory while in COPD they are both inspiratory and expiratory.

Rhonchi may be generalized as in asthma and COPD or localized due to partially obstructed bronchus as a result of fixed lesion such as tumor or foreign body.

CAUSES OF RHONCHI OR WHEEZE ON AUSCULTATION	
Generalized	Asthma Chronic bronchitis Emphysema Left ventricular failure
Localized	Bronchiolitis Tumour Foreign body

Crepitations

Crepitations are bubbling sounds.

Coarse crepitations: They may be produced by the bubbling of air through secretions in:

- Major and dilated bronchi (as in bronchiectasis).
- Pulmonary cavities.

These crepts are coarse and either decrease in number or disappear temporarily after coughing.

Fine crepitations: these crepitations are produced by explosive reopening, during inspiration, of peripheral small airways which have become occluded during expiration.

These fine crepitations do not disappear or change with coughing and are more marked in lower parts of lung. They occur in parenchymal lung diseases such as allergic and fibrozing alveolitis, interstitial pulmonary edema, early pneumonic consolidation and miliary tuberculosis. They are audible mainly during the second half of inspiration (end inspiratory).

CAUSES OF CREPITATIONS OR CRACKLES	
End inspiratory crackles Pulmonary edema (e.g. LVF) Fibrosing alveolitis Asbestosis	Typically bilateral basal
Early inspiratory and expiratory Bronchiectasis Chronic bronchitis	Localized coarse
Inspiratory Pneumonia	Localized

Pleural rub

Pleural rub is a leathery or creaking sound produced by movement of the visceral pleura over the parietal pleura, when both surfaces are roughened as by fibrinous exudates. Rub is heard at two separate stages in the respiratory cycle towards the end of inspiration and just after the beginning of expiration, best heard when the patient takes deep breathing. Pleural rub is heard over the areas of pleurisy.

Vocal resonance

Ask the patient to say ninety-nine while you listen over each part of the chest. Over consolidated lung the numbers will become clearly audible while over normal lung the sound is muffled. If vocal resonance is present, bronchial breathing is likely to be heard. Sometimes vocal resonance is increased to such an extent that whispered speech is distinctly heard, this is called *whispering pectoriloquy*.

GENERAL PHYSICAL EXAMINATION RELATED TO RESPIRATORY SYSTEM

General physical examination mainly comprises examination of hands and head.

Appearance

1. Watch the patient for signs of dyspnea at rest such as tachypnea (respiratory rate more than 14 breaths/min) and use of accessory muscle. Sternocledomastoid, scalenius and trapezius act as accessory muscle during inspiration while the abdominal muscles and lattisimus dorsi during expiration.

2. Look the pattern of breathing such as:

- Cheyne- *Stokes (Chain Stokes) breathing* periods of apnea alternate with periods of hyperpnoea seen in brain damage (due to cerebral hemorrhage or trauma).
- *Kussmaul's breathing* – deep and rapid respiration due to stimulation of respiratory center as seen in metabolic acidosis (e.g. due to ketoacidosis or uremia)
- *Hyperventilation* – rapid and shallow breathing resulting in alkalosis and tetany usual cause is anxiety.
- *Ataxic breathing* – irregular in time and depth seen in brain stem damage.

3. Character of cough and contents of sputum
4. Stridor and hoarseness

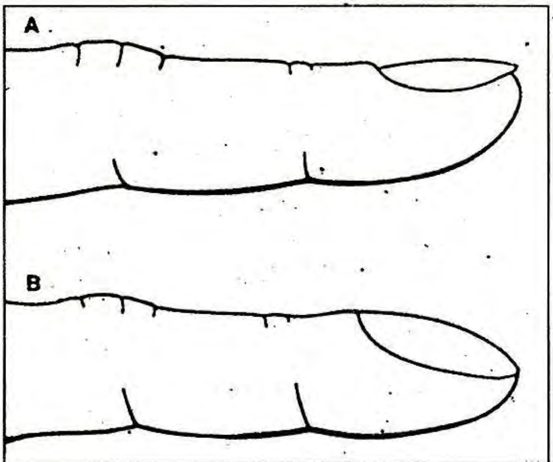
Hands

Clubbing

Clubbing is the swelling of the distal parts of the fingers or toes due to an increase in the soft tissues. Exact mechanism is unknown. It is suggested that in response to hypoxemia, an unknown humoral substance is released that causes dilatation of vessels of fingertips or toes leading to interstitial edema and swelling of subcutaneous tissue. It usually appears first in index finger. It should be noted that COPD does not cause clubbing, if any patient of COPD has clubbing then rule out the malignancy. Clubbing in tuberculosis is very rare.

There are four grades of clubbing.

I. Obliteration of angle of nail bed.
II. Fluctuation of nail bed.
III. Increased curvature of nail, especially in its long axis.
IV. Drumstick appearance: swelling of pulp of finger in all its dimensions.



Note the difference between A. normal and B. clubbing with loss of nail bed angle and increased curvature of nail.

CAUSES OF FINGER CLUBBING

Respiratory

- Bronchial carcinoma
- Presence of intrathoacic pus
  - Bronchiectasis
  - Empyema
  - Lung abscess
- Fibrosing alveolitis

Cardiovascular

- Cyanotic congenital heart diseases
- Infective endocarditis

Gastrointestinal

- Cirrhosis of liver
- Ulcerative colitis
- Crohn's disease
- Celiac disease

Congenital

- Familial clubbing

Hypertrophic pulmonary osteoarthropathy

In a few cases clubbing is associated with hypertrophic pulmonary osteoarthropathy, characterized by periosteal inflammation at the distal ends of long bones especially involving the wrist, ankle, metacarpal and metatarsal bones with radiographic evidence of subperiosteal new bone formation.

Tar staining

Look for staining of nails due to tar that results from cigarette smoking.

Flapping tremor

Ask the patient to dorsiflex the wrist with arm outstretched and to spread finger. A flapping tremor occurs in severe carbon dioxide retention in COPD.

Head & neck

Congestion and edema

Superior vena caval obstruction (mostly a complication of bronchogenic carcinoma) causes puffiness of face, distension of jugular veins, congestion of face and edema of conjunctiva (chemosis). Corpulmonale (right – sided heart failure due to pulmonary pathology)_ manifest as raised JVP, tender hepatomegaly and pedal edema.

Cyanosis

- Central cyanosis is best detected by inspecting the tongue. Central cyanosis is seen on tongue, lips and nails while the peripheral cyanosis is only seen in the nail and never presents on tongue.
- Cyanosis becomes evident when the absolute concentration of deoxygenated hemoglobin is 5 g/dl of blood.
- Cyanosis is usually obvious when the arterial oxygen saturation falls below 90% in a person with normal hemoglobin. In patients with anemia, cyanosis does not occur until even greater levels of arterial deoxygenated blood is present.
- Respiratory causes of central cyanosis are COPD, asthma, pneumonia, pulmonary infarction and excessive pulmonary fibrosis.

Lymph nodes

Examine the cervical and superaclavicular lymph nodes that may be involved in carcinoma, lymphoma and tuberculosis.

CAUSES OF CENTRAL CYANOSIS
(Arterial PaO_2 is reduced)

Acute
- Severe pneumonia
- Severe asthma
- Pulmonary edema
- Pulmonary embolism

Chronic
- COPD
- Pulmonary fibrosis
- Right to left cardiac shunt
- Polycythemia
- Hemoglobin abnormalities
- Methemoglobinemia
- Sulphemoglobinemia

CAUSES OF PERIPHERAL CYANOSIS
Arterial PaO_2 is normal

- All causes of central cyanosis cause peripheral cyanosis
- Exposure to cold
- Shock
- Arterial or venous obstruction
- Vasoconstriction such as in Raynaud's phenomenon

EXAMINATION OF RESPIRATORY SYSTEM

Examination of chest

Inspection

- *Shape of chest:* normal, barrel, pigeon, funnel, Harrison sulcus, kyphosis.
- *Lesions of chest wall*: scars of surgery or chest tube, prominent veins.

Breathing

- Respiratory rate
- Pattern of breathing: normal, Kussmaul, Chyne- Stokes or ataxic.
- Mode of breathing: abdominothoracic or thoracoabdominal.
- Chest movements: unilateral or bilateral diminished chest wall movements.

Palpation

- Apex beat
- Trachea
- Chest movements
- Chest expansion
- Tactile vocal fremitus

Percussion

Normal resonant, hyper-resonant, dull or impaired, stony dull.

Auscultation

- Quality of breath sounds; vesicular, bronchial or amphoric.
- Intensity of breath sounds: normal, reduced.
- Added sounds: rhonchi, crepitations, pleural rub, vocal resonance.

General physical examination related to respiratory system

General appearance

- Dyspnea, tachypnea
- Use of accessory muscles
- Pattern of breathing

Hands

- Clubbing
- Cyanosis
- Staining of nails
- Flapping tremor

Head and neck

- Congestion and edema
- Cyanosis
- Cervical and supraclavicular lymph nodes

INVESTIGATIONS IN RESPIRATORY DISEASES

SPUTUM

Color

- Yellowish green indicates inflammation (infection or allergy).
- Presence of blood suggests acute infection, tuberculosis, tumor, pulmonary infarct.

Sputum Gram staining and culture are indicated in:

- Lower respiratory tract infection (pneumonia).
- Aspergillus lung disease.

Sputum AFB (acid fast bacilli)

For tuberculosis, samples of early morning are sent three consecutive days.

Sputum cytology

Sputum cytology required for diagnosis of bronchogenic carcinoma. If patient is not producing sputum, it can be induced by inhalation of nebulized hypertonic saline. It can also be obtained during bronchoscopy in bronchial washing.

CHEST X-RAY

- Postero-anterior (PA) view is the routine film.
- Antero-posterior (AP) is taken if the patient is unable to stand. Cardiac shadow is larger in AP view.
- Lateral view is required to localize the site of abnormality visible on PA view.
- Lordotic view is required to look lung apices as in pulmonary tuberculosis.
- Lateral decubitus view is taken to confirm pleural effusion.
- Chest x-ray should be taken in full inspiration, if taken in expiration lower parts of lungs are not clear.
- X-ray reading should be in sequence (inside to outside) starting from trachea to mediastinum, heart, hila, diaphragm, costophrenic angle, cardiophrenic angle, lung apices, lung parenchyma, pleural space, skeleton and then soft tissues.

It is better to look the name, date, position of patient and quality of x-ray but due to shortage of time, examiners usually do not like that students start from these features, therefore start from saying " x-ray chest PA view showing ------- radiological details, not straight forward diagnosis.

Following points should be noted in chest X-ray:

Trachea
Central or deviated

Mediastinum
- Look for the widening of mediastinum
- Shifting of mediastinum due to pull or push phenomenon.

Heart
Size, shape and position of heart, aortic knuckle.

Hilar shadow
- Size and shape of hilar shadow, prominent hilar lymphadenopathy unilateral or bilateral.
- Pulmonary artery shadow

Diaphragm
- Elevated or flat.
- Gas under the right diaphragm indicates gut perforation.
- Obliteration of costophrenic angle – in pleural effusion.

Lung field
- Lung apices for haziness due to tuberculosis.
- Homogenous or patchy infiltrates.
- Reticulonodular pattern of tuberculosis
- Fibrosis
- Cavities, bullae
- Prominent vascular markings.
- Round opacities.

Pleural space
- Wide pleural space, no lung marking in pneumothorax.
- Pleural thickening

Skeletal deformities
Bony deformities, fracture.

Soft tissue shadow
Look for subcutaneous emphysema

CT SCAN
- CT scan demonstrates size and position of a pulmonary nodule or mass (such as malignancy) and whether calcification or cavitation is present in it.
- CT scan is also valuable in bronchial carcinoma staging, to demonstrate mediastinal, pleural or chest wall invasion.
- High – resolution CT scanning involves sampling the lung parenchyma with thin 1-2 mm thickness throughout the lung. It is particularly effective in the diagnosis of interstitial lung disease, bronchiectasis and emphysema.

VENTILATION-PERFUSION SCAN
Ventilation – perfusion (V/Q) scan is required for the diagnosis of pulmonary embolism in which there is diminished perfusion relative to ventilation.

ULTRASOUND
It is required for detection of pleural effusion especially that is loculated.

MEDIASTINOSCOPY
The mediastinoscope is introduced through a small incision at the suprasternal notch to give a view of upper mediastinum. Biopsy of some mediastinal nodes is possible and will reveal the presence or absence of malignant cells in the enlarged lymph nodes previously detected by CT, allowing accurate staging of the disease.

PLEURAL ASPIRATION AND BIOPSY
Pleural aspiration is carried out for diagnostic purpose and for therapeutic purpose when large effusion causes breathlessness. For diagnostic purpose a 10 ml syringe is inserted through intercostals space over the area of dullness and fluid is withdrawn. Samples are sent for D/R, C/S, and cytology.

- For drainage of large amount of effusion "three way" needle is used.
- Pleural biopsy is performed with Adam's needle.

DR= Detailed Report: usually including cell count and biochemistry.

PROCEDURE OF THERAPEUTIC PLEURAL ASPIRATION

- Carefully sterilize the skin over the aspiration site. Sterile gloves, cap, gown and mask must be worn.
- Anaesthetize the skin, muscle and pleura with 2% lignocaine.
- Make a small incision, then push a 28 French gauage Argyle catheter into the pleural space.
- Attach to three-way tap and 50 mL syringe.
- Aspirate up to 1000 mL. Stop aspiration if patient becomes uncomfortable -- shock may ensure if too much fluid is withdrawn too quickly.

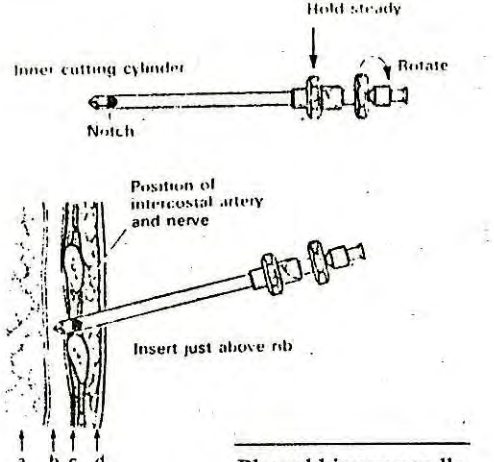
Pleurodesis
Tetracycline 500 mg or bleomycin 15 units in 30-50 mL sodium chloride 0.9% solution is instilled into the pleural cavity to achieve pleurodesis in recurrent/malignant effusion.

PROCEDURE OF PLEURAL BIOPSY

- Pleural biopsy is usually performed after the aspiration of diagnostic fluid samples but before draining large volumes of fluid.
- A small skin incision is made, as the end of the Adam's pleural biopsy needle is fairly blunt.
- Once in place through the pleura, the back part of the needle is rotated to open the notch; this is kept pointing forward.
- With lateral pressure the needle is withdrawn so that the notch will snag against the pleura.
- The needle is held firmly and the hexagonal grip is twisted clockwise to cut the biopsy. To avoid damage to the intercostals vessel or nerve, the notch should never be directed upwards when the biopsy is taken.
- Several biopsies should be taken at different angles by repeated insertion of the needle.
- Specimens should be put in sterile saline for culture for tuberculosis and into 10% Formaline solution for histological examination.

Complications of pleural aspiration

- Pleural shock: due to vagal stimulation as a complication of pain.
- Air embolism
- Pulmonary edema: if fluid is removed too quickly.
- Pneumothorax: if lung is ruptured.
- Empyema: if introduction of infection into pleural space.
- Rupture of intercostals vessels.



Pleural biopsy needle

FIBREOPTIC BRONCHOSCOPY

There are two types of bronchoscopes; flexible fiberoptic and rigid type. Flexible bronchoscope is commonly used and requires only local anesthetic solution while rigid type requires general anesthesia.

- Trachea and large bronchi are inspected; distortion or obstruction can be seen.
- Abnormal tissue in the bronchial lumen or wall can be biopsied.
- Bronchial brushing, washings or aspirates can be taken for cytological or bacteriological examination.

Indications

- Lesion requiring biopsy seen on x-ray chest
- Hemoptysis
- Stridor
- Positive sputum cytology for malignant cells with no chest X-ray abnormality
- Collection of bronchial secretions for bacteriology, especially tuberculosis
- Recurrent laryngeal nerve palsy of unknown etiology
- Infiltrative lung disease (to obtain a transbronchial biopsy)
- Investigation of collapse lobes or segments
- Aspiration of mucus plug.

Procedure

After overnight fasting atropine 0.6 mg IM given 30 min before procedure.topical 2% lignocaine gel is applied to nose, nasopharynx, and pharynx. IV sedation with diazepam 10mg. Bronchoscope is passed through the nose, nasopharynx, and pharynx under direct vision. Lignocaine 2ml of 4% is dropped through the instrument on to the vocal cords. Bronchoscope is passed through the cords into the trachea. All segments and subsegmental orifices should be identified. Biopsies and brushing should be taken.

PULMONARY FUNCTION TESTS (PFTs)

Pulmonary function tests measure the ability of the respiratory system to perform gas exchange by assessing its ventilation, diffusion & mechanical properties.

PULMONARY FUNCTION TESTS
Airflow rates (expiratory flow rate)
Lung volumes
Gas transfer factor (diffusing capacity)

Expiratory flow rate

Expiratory flow rate is the maximal rate of airflow during forced expiration. It is mainly influenced by lung volume and by effort. Other influencing factors on flow rate are elastic recoil of lung, small peripheral airway resistance and cross sectional area of larger central airways. Expiratory flow rate is measured by spirometry.

Lung volumes

Lung volumes are the volumes of various intrapulmonary compartments. It is measured by use of spirometry and either helium dilution or body plethysmography.

Diffusing capacity

It is the efficiency of gas transfer from alveoli to pulmonary capillary bed. It is determined by measuring the amount of carbon monoxide transferred from alveolar gas to pulmonary capillary bed after the patient inhales a known amount of carbon monoxide. It is severly reduced in emphysema and lung fibrosis.

INDICATIONS OF PULMONARY FUNCTION TESTING

- Assessment of type and extent of lung dysfunction.
- Diagnosis of causes of dyspnea and cough.
- Detection of early evidence of lung dysfunction.
- Monitoring for occupational lung diseases
- Follow-up of response to therapy.
- Preoperative assessment.

CONTRAINDICATIONS

- Acute severe asthma
- Respiratory distress (because many tests require effort)
- Angina
- Pneumothorax
- Ongoing hemoptysis

Spirometry and measurement of lung volumes allow measurement of presence and severity of obstructive and restrictive pulmonary dysfunction.

SPIROMETRY

The spirometer measures the forced expiratory volume in one second (FEV_1) and the forced vital capacity (FVC). The technique involves a maximum inspiration followed by a forced expiration into the spirometer. The act of expiration triggers recording of chart which measures lung volume against time (in seconds).

The patient is asked to take in as deep as possible and then expel it as hard and as fast as possible. If the forced expiration is made into a recording spirometer, the forced expiration volume in the standard time of 1 second (FEV_1) can be measured.

Now measure the volume of gas that can be forcefully expelled from the lungs after maximum inspiration i.e. forced vital capacity (FVC).

The ratio of these two volumes may be expressed as a percentage (FEV_1 / VC %). Normal person can expel between 65 to 85% of the VC in 1 second.

In obstructive lung disease e.g. asthma and COPD this ratio is reduced. It means in given time (1 sec) rate of pulmonary airflow becomes reduced. Now decide. whether the obstructive pattern is reversible as in asthma or irreversible as in COPD. Give bronchodilater inhaler such as Ventolin, if there is improvement in FEV_1 after 10-20 min more than 15%, it indicates asthma. In COPD there is usually no or little improvement.

In restrictive lung disease e.g. interstitial lung disease, FEV_1 and VC are reduced in the same proportion and the ratio remains normal.

The test describes whether the disease is obstructive or restrictive. Benefit of this diagnosis is that obstructive pulmonary disease can be reversed by brounchodilators however absence of improvement in PFTs with bronchodilator does not rule out successful clinical response to bronchodilator therapy.

VALUES OBTAINED FROM THE SPIROGRAM	
Tests	**Definitions**
Tidal volume (VT)	The volume of air in one breath during normal quiet breathing (normal value: 500-800 ml)
Vital capacity (VC)	The volume of gas that can be forcefully expelled from the lungs after maximal inspiration.
Forced vital capacity (FVC)	The volume of gas that can be forcefully expelled from the lungs after maximal inspiration. It is same as VC but inspiration is more forceful and rapid.
Forced expiratory volume in 1 second (FEV_1)	The volume of air expelled in the first second of the FVC maneuver. It primarily reflects the status of large airways. (normal = 75% of VC)
FEV1/FVC	The normal ratio of FEV1 to FVC is > 70%. If only FEV1 is low – shows obstructive pattern; if both FEV1 and VC are low—show restrictive pattern
Peak expiratory flow rate (PEFR)	The forced expiratory flow rate over middle half of the VC (normal is 25-75% of VC).It reflects the status of the small airways

LUNG VOLUMES	
These volumes require use of spirometry and either helium dilution or body plethysmography	
Total lung capacity (TLC)	The volume of gas in the lungs after maximal inspiration. In emphysema and asthma TLC is increased but FVC is reduced.
Functional residual capacity (FRC)	The volume of gas in the lungs at the end of a normal tidal expiration
Expiratory reserve volume (ERV)	The volume of gas representing the difference between functional residual capacity and residual volume.
Residual volume (RV)	The volume of gas remaining in the lungs after maximal expiration.

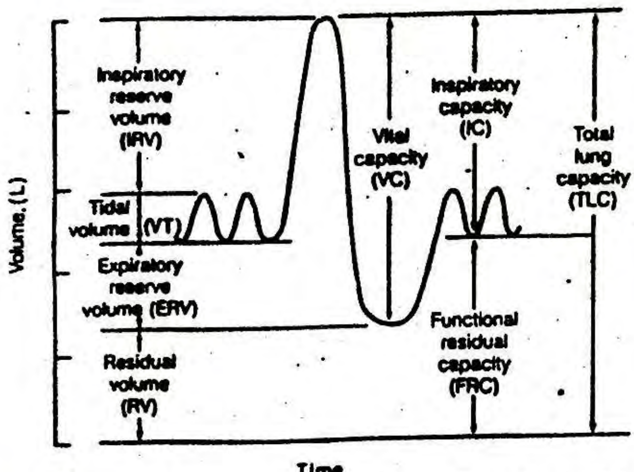


Figure 2-1. The subdivisions of lung volume as recorded by a spirometer. The record is generated on paper calibrated for volume in the vertical direction and time in the horizontal. The term "capacity" is applied to a subdivision composed of two or more volumes.

PEAK EXPIRATORY FLOW RATE (PEFR)

This is an extremely simple and cheap test. It describes maximal airflow rate in a given time. Patient is asked to take a full inspiration to total lung capacity and then blow out forcefully into the peak flow meter which is held horizontally.

Normal person can empty their chest from full inspiration in 4 sec or less, prolongation of the forced expiratory time to more than 6 sec indicates airflow obstruction. Peak flow meter is best for monitoring the progression of disease, patient can assess his airflow limitation at home and can take treatment accordingly.

It is very simple and cheap test. Patient is asked to take a full inspiration to total lung capacity and then blow out forcibly

PATTERNS OF ABNORMAL VENTILATORY CAPACITY			
	Asthma	**Emphysema**	**Lung fibrosis**
VC	Low	Low	Low
FEV1	Low	Low	Low
FEV1/VC	Low	Low	Normal
RV	High	High	Low
TLC	High	High	Low
DLCO	Normal	Low	Low

VC= vital capacity
FEV1= forced expiratory volume in 1 sec
DLCO= diffusing capacity for carbon monoxide
TLC= total lung capacity
RV= residual volume

ARTERIAL BLOOD-GAS ANALYSIS (ABGs)

Measurement of PO2 and PCO2 and H+ concentration in arterial blood is valuable in assessment of hypoxemia or acid-base balance in respiratory failure, and asthma.

Procedure

- Heparinize the syringe with 0.1 ml heparin to prevent clot formation.
- Draw blood from radial or brachial or femoral artery.
- The sample should be immersed in ice bag immediately to prevent metabolism that can reduce PO_2 and increase PCO_2.

Normal values

PH: 7.35-7.45
PO_2: 75-100 mmHg
PCO_2: 36-46 mmHg
HCO_3: 22-26 mmol/L
O_2 saturation: 95-100%

Primary respiratory acidosis

- High PCO2 and low pH
- Causes are type II respiratory failure (due to COPD and hypoventilation).

Compensated respiratory acidosis

High PCO2 but pH becomes normal as the kidney starts to compensate with renal bicarbonate retention. Therefore the patient presents with primary respiratory acidosis (raised PCO2), normal pH, and compensatory metabolic alkalosis (raised bicarbonate).

Primary respiratory alkalosis

- Low PCO2 and high pH.
- Causes are hyperventilation intentionally or unintentionally.

Compensated respiratory alkalosis

Low PCO2, normal pH and low bicarbonate as a compensatory response from the kidney.

Primary metabolic acidosis

- Low bicarbonate, low pH.
- Causes are chronic renal failure, diabetic. ketoacidosis and lactic acidosis.

Compensated metabolic acidosis

Lungs try to maintain pH to normal by rapid respiratory rate, blowing off CO2 and causing respiratory alkalosis. Therefore the picture is low bicarbonate, almost normal pH and low CO2.

COMMON RESPIRATORY SYMPTOMS

COUGH

Noisy expulsion of air from lungs, at once is known as cough.

Causes

Acute (< 3 weeks)

- Upper respiratory viral or bacterial infection such as common cold and acute bronchitis.
- Other causes are acute asthma, pneumonia, pulmonary embolism and pulmonary edema.

Chronic

- Chronic bronchitis (smoker's cough)
- Postnasal drip, gastroesophageal reflux disease
- Chronic bronchial asthma
- Tuberculosis
- Interstitial lung disease
- Bronchogenic carcinoma
- ACE inhibitors

Treatment

Eliminate irritant exposure such as tobacco smoke, occupational agents and discontinue ACE inhibitors and beta- blockers.

Treatment of the cause

- *Common cold:* antihistamine and decongestant combination.
- *Asthma*: bronchodilators and corticosteroids.
- *Postnasal drip:* intranasal steroid spray such as Nasacort AQ

Symptomatic treatment

Dry cough

Syp. Actified DM
Syp. Pholcodine
Syp. Davenol
Syp. Tixylix
Syp. Sancos
Syp: Benatuss
Syp. Hydryllin DM

Productive cough: (Expectorants)

Syp. Hydryllin
Syp. Benadryl
Syp. Reltus
Syp. Histamol-D

SPUTUM

Color	Types of sputum
White	Mucoid
Grey	Mucoid (dust inhalation)
Black	Mucoid + coal dust (melanoptysis)
Yellow or green	Purulent
Rusty	Altered blood (pneumococcal pneumonia)
Pink frothy	Pulmonary edema
Blood-stained	Hemoptysis

Examination of sputum

Quantity

- Scanty: Bronchitis, early stage of pneumonia, asthma.
- Moderate amount: Chronic bronchitis, tuberculosis.
- Large amount: Bronchiectasis, chronic bronchitis, and lung abscess.

Appearance

- Watery: Pulmonary congestion, pulmonary edema
- Mucoid: Acute & chronic bronchitis, asthma
- Mucopurulent: All infections of lungs & bronchi
- Purulent: Bronchiectasis, lung abscess, pulmonary tuberculosis

Color

- Blackish: due to inhalation of carbon
- Rusty (khaki): due to altered blood mixed with sputum in lobar pneumonia
- Reddish: indicates hemoptysis
- Frothy pink: in pulmonary edema
- Sticky brown to red: in Klebsiella infection

HEMOPTYSIS

The expectoration of blood or blood stained sputum is known as hemoptysis. The source of blood should be below the vocal cords. The lungs are supplied with dual circulation; pulmonary arteries arise from right ventricle and supply pulmonary parenchyma while the bronchial arteries arise from aorta or intercostals arteries and supply airways, blood vessels, hila and visceral pleura. The bronchial circulation is only 1-2% of total pulmonary blood flow but is more common source of bleeding. Bonchial blood flow dramatically increases in inflammation.

Causes

From airways in

- Bronchitis
- Bronchiectasis
- Bronchial adenoma
- Bronchogenic carcinoma

From pulmonary vasculature

- Mitral stenosis
- Pulmonary infarction
- Left ventricular failure
- A-V malformation

From pulmonary parenchyma

- Pneumonia
- Bleeding disorders
- Autoimmune diseases e.g. Goodpasture's syndrome and Wegner's syndrome

Massive hemoptysis: more than 200-600 ml of blood in 24 hours. Occurs in bronchiectasis, tuberculosis, pulmonary infarction.

Investigations

- *X-ray chest:* for tuberculosis, bronchogenic carcinoma, pulmonary infarction.
- *Blood CP & Platelets*: to look for hemoglobin level and platelet count; as thrombocytopenia can also cause hemptysis.
- *Bleeding time, clotting time & prothrombin time*
- *Bronchoscopy*: in high risk persons for carcinoma of lung such as chronic smokers.
- *High resolution CT:* to diagnose bronchiectasis and arterio-venous malformations.

DIAGNOSIS OF HEMOPTYSIS AND HEMATEMESIS

Hemoptysis	Hematemesis
Cough precedes hemorrhage	Nausea and vomiting precede hemorrhage
Blood frothy from admixture with air	Generally airless
Sputum bright red in color and may be stained for days	Blood often altered in color by admixture with gastric contents, usually dark red or brown
History suggests respiratory disease	Previous history of indigestion
Confirmed by bronchoscopy	Confirmed by gastroscopy

Treatment

- Treatment of the cause
- *Resuscitation*
  - Airway must be protected, ventilation ensured.
  - Circulation is maintained with blood, plasma expanders.
- *Bronchoscopy:* uncontrolled bleeding needsflexible or rigid bronchoscopy and surgical consultation.
- *Angiography* to localize the site of bleeding and to embolize the source (bronchial artery) that is effective in 85% of cases.

Symptomatic management

- Reassurance
- Sedation with Tab. Diazepam (Valium) 5mg to reduce fear.
- Antibiotics to prevent secondary infection
- Clotting agent e.g. Tranexamic acid (Transamin) – Caps 250mg / 500mg 3-4 times daily Inj. 250mg 2-4 amps daily IV or IM.

DIFFERENTIAL DIAGNOSIS OF CHEST PAIN

Majority of patients with chest pain consult cardiologists and it is necessary for the doctor to consider all aspects of chest pain including pleurisy, dyspepsia and musculoskeletal pain.

Lung / pleura
- Pneumothorax
- Pleurisy

Cardiac
- Angina: stable or unstable
- Myocardial infarction
- Pericarditis

Musculoskeletal
- Local tenderness common

Esophageal
- Esophageal spasm
- Esophagitis

Aortic
- Dissecting aneurysm (tearing pain in back, asymmetric pulses, bradycardia)

SHORTNESS OF BREATH (DYSPNEA)

Shortness of breath is an unpleasant subjective awareness of the sensation of breathing. Patient usually feels discomfort either from increased ventilatory drive or reduced ventilatory capacity.

Increased ventilatory drive causing increased respiratory rate occurs in:

- Fever
- Exercise
- Acidemia: ketoacidosis, lactic acidosis, uremia
- Hypoxia: asthma, COPD, cyanotic heart diseases.
- Hypercarbia: COPD

Reduced ventilatory capacity occurs in:

- Reduced lung volume in pneumonia, pulmonary edema and interstitial lung disease.
- Pleural pain.
- Increased resistance to airflow in asthma, COPD, laryngeal obstruction.

PATIENT EVALUATION

History

- Ask about cardiac and respiratory risk factors such as:
  - Diabetes, hypertension, smoking for heart disease.
  - Asthma, COPD and tuberculosis for respiratory disease
  - Renal disease for uremia
  - Medication for lactic acidosis.
- History of previous similar episodes and their diagnosis.
- Associated features such as palpitation, syncope, chest pain, nausea, vomiting and sweating are cardiac manifestations while cough, chest pain related to breathing, sputum are features of respiratory disease and low urine output and anemia indicate renal disease.
- In acute dyspnea, rule out cardiac failure, heart block, MI, angina, pulmonary embolism, pneumothorax and laryngeal edema.
- Chronic dyspnea is progressive i-e patient's working capacity gradually decreases. *Chronic episodic dyspnea* occurs in asthma, heart failure, acute or chronic bronchitis and recurrent pulmonary embolism. *Chronic constant dyspnea* occurs in COPD, pulmonary fibrosis and pulmonary hypertension.

Examination

Quick and relevant examination related to cardiac disease such as pulse showing tachycardia, bradycardia, irregular pulse, displaced apex beat, murmurs and basal crepts.

Respiratory examination such as rapid respiratory rate, abnormal percussion note, wheeze, crepts or pleural rub.

Investigations

ECG, chest X-ray, ABGs, RBS, urea and creatinine are usually enough for diagnosis.

SHORTNESS OF BREATH (DYSPNEA)		
System	**Acute dyspnea at rest**	**Chronic exert ional dyspnea**
Cardiovascular	• Acute pulmonary edema • Myocardial ischemia (angina may present just with dyspnea and this presentation is called angina equivalent)	• Chronic heart failure • Myocardial ischemia (angina may present just with dyspnea and this presentation is called angina equivalent)
Respiratory	• Pneumothorax • Pulmonary embolism • Laryngeal edema (as an anaphylaxis reaction, a common complication of ACE inhibitors and other drugs) • Acute severe asthma • Acute exacerbation of COPD • Acute respiratory distress syndrome • Pneumonia • Inhaled foreign body • Respiratory muscle weakness (in myasthenia gravis) and paralysis (in Guillain – Barre syndrome)	• COPD • Chronic asthma • Bronchogenic carcinoma • Large pleural effusion • Chronic pulmonary embolism • Interstitial lung diseases such as: – Fibrosing alveolitis – Sarcoidosis – Extrinsic allergic alveolitis – Pneumoconiosis
Others	• Metabolic acidosis due to: – Renal failure – Diabetic ketoacidosis – Lactic acidosis • Psychogenic: hyperventilation syndrome due to anxiety	• Severe anemia • obesity

RESPIRATORY FAILURE

When the normal pressures of oxygen and carbon dioxide in the arterial blood are no longer maintained, the condition is called respiratory failure. For practical purposes this means the finding of PaO2 of less than 60 mm Hg or a PaCO2 of more than 50 mm Hg.

TYPES

TYPE 1 RESPIRATORY FAILURE:

In type I or acute hypoxemic failure $PaCO_2$ is normal or low but PaO2 is reduced i.e. there is hypoxemia but no hypercapnia (CO_2 retention). To remember we can say that in type I there is one problem that is hypoxemia. Type I failure occurs with diseases that damage lung tissue.

Causes:

- Severe bronchial asthma (type II failure when life-threatening).
- Acute exacerbation of COPD (also causes type II respiratory failure).
- Pneumonia
- Left ventricular failure and other causes of pulmonary edema.
- Pulmonary embolism
- Acute respiratory distress syndrome.
- Pneumothorax
- Interstitial lung disease & fibrosing alveolitis.

Arterial blood gases

- PaO_2: very low
- $PaCO_2$: normal or low
- pH: normal or low
- HCO_3: normal

Treatment:

Acute type I respiratory failure:

- Treatment of underlying cause e.g. pulmonary edema, pneumonia, acute respiratory distress syndrome.
- Oxygen in high concentration (> 35%) by oronasal mask.
- Tracheal intubation and mechanical ventilation may be required.
- Opiates may be given in acute left ventricular failure, massive pulmonary embolism and pulmonary infarction or pneumonia to relieve pain but never use opiates in COPD and asthma.

Chronic type I respiratory failure:

- Treatment of underlying causes e.g.emphysema, interstitial lung disease & fibrosing alveolitis.
- Oxygen in high conc.

Clinical features of respiratory distress

- Use of accessory muscles, intercostals resection.
- Rapid respiratory rate
- Tachycardia
- Sweating
- Agitation, restlessness, diminished conscious level.
- Paradoxical respiration, respiratory alternans.

Monitoring in respiratory failure

Pulse oximetry:
Pulse oximeter is attached to ear lobe or finger. It shows arterial oxygen saturation. However it may be inaccurate in those patients with poor peripheral perfusion.

Arterial blood gas analysis
It gives information about oxygenation status of blood and about acid- base balance.

TYPE II RESPIRATORY FAILURE:

In type II or ventilatory failure PaCO2 is elevated and PaO2 is reduced i.e. there are two problems hypoxemia and hypercapnia leading to severe acute respiratory acidosis. Type II failure occurs in diseases in which alveolar ventilation is insufficient to excrete carbon dioxide.

Causes:

<u>*Acute type II*</u>

- COPD (most common cause)
- Depression of respiratory center by narcotics or sedatives.
- Exhaustion of respiratory muscles such as in life-threatening acute severe asthma.
- Respiratory muscle paralysis (in Guillain Barre syndrome)
- Rib fracture
- Inhaled foreign body
- Sleep apnea syndrome

<u>*Chronic type II*</u>

- COPD
- Ankylosing spondylitis
- Kyphoscoliosis

Signs of carbon dioxide retention

- Warm periphery
- Bounding (high volume pulse)
- Flapping tremor (asterixis)
- Papilledema
- Altered level of consciousness
- Myoclonic twitching of muscles, tremor

Arterial blood gases

- PaO_2: low
- $PaCO_2$: high
- pH: low
- HCO_3: normal

Common causes of hypercapnia (raised PCO2)

- COPD
- Central sleep apnea
- Brainstem lesion
- Myasthenia gravis
- Peripheral neuropathy
- Myopathy
- Ankylosing spondylitis kyphoscoliosis trauma

Management

Treatment of the underlying causes. Mechanical ventilation required if the condition causing respiratory failure could not immediately be reversed. Barotrauma is the main complication of mechanical ventilation.

Maintenance of airway, regular suction and frequent chest physiotherapy.

Most common cause is acute exacerbation of COPD and treatment includes low concentration oxygen, bronchodilators, broad-spectrum antibiotics and diuretics.

Give low dose oxygen by nasal canulla (1-3 L/min) or Venturi mask (24-28%). The aim of oxygen therapy is to achieve PaO2 about 60 mmHg and oxygen saturation > 90% that ensures adequate oxygenation of vital organs.

If PaCO2 continues to rise or PaO2 is not maintained without hypercapnea and academia, mechanical ventilatory support should be offered early. Decision of mechanical ventilation is often late due to some hope of improvement with medication, non- availability of ventilator or due to non- affordability of patient.

Oxygen therapy

There are two drives or stimulations to respiratory center in brain, hypoxia and hypercapnea. Brain becomes insensitive to persistent hypercapnea in COPD and the only drive in these patients is hypoxia that stimulates respiratory center.

High concentration of oxygen can cause deterioration because it reduces the hypoxic drive to breathing in patients whose central (brain stem) response to CO2 is diminished or absent. Oxygen is given to reduce hypoxia but it should be in low dose therefore there should be no total correction of hypoxia and no loss of hypoxic drive. Aim of oxygen therapy is to raise PO2 55-60 mmHG. Repeat ABGs and if the PCO2 is increasing and pH is decreasing with oxygen therapy, mechanical ventilation is advised.

Adverse effects of oxygen therapy

100% oxygen is irritant ant toxic if inhaled for more than a few hours. Premature infants develop retrolental fibroplasias and blindness if exposed to excessive concentration. In adults it causes pulmonary edema if given in high doses for more than 24 hours.

Experience sharing

Smoking is a major risk factor for ischemic heart disease and cardiac failure as well as COPD. This is not uncommon that many patients have both conditions simultaneously; cardiac failure and COPD. In these patients correct diagnosis is critical and oxygen therapy is given very cautiously.

Middle aged man of 55 years came to casualty with shortness of breath and some drowsiness, he was considered as a case of left ventricular failure (LVF) by a junior doctor and high dose oxygen was started along with IV frusemide. When there was no improvement, instead deterioration started with unresponsiveness, then he called a senior doctor who properly examined the patient. Chest was not so bad and findings were not matching with severe LVF. Dyspnea and drowsiness was due to acute exacerbation of COPD. ABGs were performed that showed type II respiratory failure. Ventilator was arranged for him but he did not survive and died before getting mechanical ventilation. Cause of death was high concentration oxygen.

MECHANICAL VENTILATION

When the patient continues to deteriorate or fails to improve with other measures and oxygen therapy, he needs some respiratory support with mechanical ventilation. Mechanical ventilation improves CO2 elimination and removes work of breathing, gives relief from exhaustion by giving rest to the respiratory muscles.

TYPES

Mechanical ventilation may be non- invasive or invasive.

Non- invasive mechanical ventilation

In non- invasive respiration is supported with face mask or nasal mask so that endotracheal intubation is avoided. Patient should be conscious, cooperative, be able to breath spontaneously and cough effectively. This technique is commonly used in acute exacerbation of COPD and pneumonia.

Invasive mechanical ventilation

In invasive mechanical ventilation endotracheal tube is passed. Patient may require full or partial support. In full support all respiration is controlled by ventilator that does not allow spontaneous breaths. Patient is deeply sedated with short acting IV anesthetic agent and paralyzed with muscle relaxant. In partial support ventilator helps and augment patient's own breaths; it does not require deep sedation and paralysis.

INDICATIONS

- Respiratory failure not responding to medical treatment.
- Head injury – controlled hyperventilation to reduce intracranial pressure.
- Chest injury.
- Severe pulmonary edema

WEANING FROM RESPIRATORY SUPPORT

This is the process of progressively reducing and eventually removing all external ventilatory support and associated apparatus. If apparatus is suddenly removed, patient may be unable to breath because of respiratory muscle weakness and residual decreased lung compliance.

COMPLICATIONS

- Tube in one lung causes collapse of other lung.
- Fall in cardiac output due to positive pressure in lung and thorax that reduces venous return.
- Ventilator induced lung injury such as barotraumas due to over-distension of alveoli leading to pneumomediastinum, subcutaneous emphysema and pneumothorax.
- Nosocomial (hospital acquired) pneumonia.
- Abdominal distension and ileus.

MODES OF MECHANICAL VENTILATION	
NON – INVASIVE RESPIRATORY SUPPORT	
Continuous positive pressure **(CPAP)** given by mask	Used in acute exacerbation of COPD, pulmonary edema and post- operative collapse of lung. May be used with endotracheal intubation or tightly fitting face mask
Bilevel positive airway pressure **(BiPAP)**	
Non- invasive intermittent positive pressure ventilation **(NIPPV)** given by mask	Used in acute exacerbation of COPD
INVASIVE RESPIRATORY SUPPORT	
Controlled mandatory ventilation **(CMV)**	Appropriate for initial control of patient with little respiratory drive.
Synchronized intermittent mandatory ventilation **(SIMV)**	IT allows patient to breath spontaneously between the mandatory tidal volumes delivered by ventilator.
Pressure support ventilation **(PSV)**	Spontaneous breaths are augmented by a pre- set level of positive pressure (positive pressure means above atmospheric pressure)
Positive end- expiratory pressure **(PEEP)**	Pressure given throughout the expiration. Helps in re-expand collapse or edematous lung.

ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS)

Acute respiratory distress syndrome formerly known as adult respiratory distress syndrome is a group of diseases in which there is damage to the alveolar epithelium and capillary endothelium that allows the alveolar spaces to become flooded with edema of high protein contents (i.e. non-cardiogenic pulmonary edema).

SOME CONDITIONS PREDISPOSING TO ARDS

Common	Uncommon
• Gram-negative septicemia • Multiple trauma • Pneumonia (bacterial, viral, pneumocystis, mycoplasma) • Pancreatitis • Severe burns • Gastric aspiration • Perforated viscus	Multiple blood transfusion Cardiopulmonary bypass Inhaled toxic gases Fat embolisation Raised intracranial pressure Drugs, e.g. thiazides, methadone, barbiturates

CLINICAL FEATURES

- Dyspnea: occurring 12-24 hours after the inciting event.
- Labored breathing, tachypnea, intercostals retractions and crepitations all over the both lungs especially the base.
- Many patients with ARDS demonstrate multiple organ failure involving kidneys, liver, gut, CNS, and CVS.

INVESTIGATIONS

X-ray chest shows rapidly progressive diffuse or patchy bilateral fluffy or soft shadowing that characteristically spares costophrenic angles.

TREATMENT:

- Identification and specific treatment of cause (e.g. sepsis).
- Mechanical ventilation is usually required for hypoxemia.
- Crystaloid solution such as normal saline should be used when intravascular volume expansion is necessary. Dopamine may be required if cardiac output is low.
- Diuretics may be required.
- Prone position improves oxygenation as compared to supine position.
- Inhaled nitric oxide may be beneficial.
- Broad-spectrum antibiotics should be started if infection is known or suspected.

PROGNOSIS

Mortality in sepsis is 90% and in other conditions 50%.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

Chronic obstructive pulmonary disease (COPD) is a disease state characterized by presence of air flow obstruction due to chronic bronchitis or emphysema; the airflow obstruction is generally progressive. The impairment of the lung function is largely fixed but may be partially reversible by bronchodilator therapy.

Although emphysema and chronic bronchitis must be diagnosed and treated as specific disease, most patients with COPD have features of both conditions simultaneously. Chronic bronchitis is defined in clinical terms whereas emphysema is defined in pathological terms.

Chronic bronchitis

This is a clinical disorder characterized by productive cough on most of the days for at least three consecutive months for more than two successive years, providing others causes of productive cough such as bronchiectasis and untreated chronic asthma have been excluded.

Emphysema

This can be defined as abnormal and permanent dilatation of the air spaces lying beyond the terminal bronchioles accompanies by destruction of their walls is known as emphysema.

ETIOLOGY

1. Cigarette smoking is the most important cause of both chronic bronchitis and emphysema.
2. Air pollution, airway infection, familial disorders and allergy are also responsible for chronic bronchitis.
3. Alpha 1- antitrypsin deficiency have been implicated in emphysema as following:

Elastase anti-elastase imbalance

In serum anti-elastases are usually present which prevent the destruction of elastic tissues by the enzyme elastase. In normal condition, elastases & anti-elastases are balanced. It is suggested that when the elastase activity in the lung is increased due to decreased anti-elastase (alpha – 1 antitrypsin) destruction of aleveolar walls occur. Cigarette smoking increases neutrophils in the lungs which are rich in elastase and other catabolic enzymes, causing in alveolar wall damage.

PATHOLOGY

Chronic bronchitis

There is hypertrophy of the mucus-secreting glands and an increase in the number of goblet cells in the bronchi and bronchiole with a consequent decrease in ciliated cells. Therefore, there is increased mucus production and less efficient transport or clearance of the mucus in the airways. (because transport of mucus is mediated by ciliated cells which has become reduced).
Mucosal edema and permanent structural damage leads to bronchial fibrosis and reduce the caliber of the air passages. If the airway narrowing is combined with emphysema (causing loss of elastic recoil of the lung) the resulting airflow limitation is even more severe.

Emphysema

Distension and damage of lung tissue in emphysema leads to expiratory airflow limitation and air trapping. The loss of lung elastic recoil results in an increase in total lung capacity (TLC) while the loss of alveoli results in decreased gas transfer.

CLINICAL FEATURES

First of all we will discuss the clinical features of COPD due to combination of chronic bronchitis and emphysema and later on predominant features of both will be compared.

Symptoms

Cough

Initially repeated attacks of productive cough usually during winter, later on cough becomes constant. Tightness in the chest is common in the morning, before the excessive bronchial secretions are cleared by coughing.

Expectoration

Sputum may be little, mucoid and tenacious. Frankly purulent sputum is indicative of infection, which often occurs in these patients.

Dyspnoea

Dyspnoea is noted initially on heavy exertion, but as the condition progresses it occurs with mild activity and even at rest. Dyspnea is aggravated by infection, excessive cigarette smoking and adverse atmospheric conditions.

On examination

Inspection *(signs of advanced airway obstruction)*

- Patient is dyspnic
- Accessory muscles of respiration are used. Sternomastoid and scalene muscles become prominent during inspiration.
- Pursing of lips: during expiration patient closes his lips tightly to aid expiration by breathing out against a resistance in attempt to prevent air trapping by maintaining intrabronchial pressure that prevents sudden collapse of small airways during expiration.
- Reduction in the length of trachea above the sternal notch.
- Tracheal tug: tracheal descent during inspiration.
- Indrawing of supraclavicular fossae and intercostals spaces during inspiration.
- Jugular venous distension during expiration.
- Fixation of scapulae by clamping the arms at the bedside.

- Chest becomes barrel-shaped i.e. anteroposterior diameter becomes more than the transverse diameter, due to air trapping.
- Central cyanosis.

Palpation
- Apex beat not palpable
- Chest expansion becomes decreased.

Percussion
- Percussion note is hyper-resonant
- Loss of normal area of cardiac &liver dullness.

Auscultation
- Breath sounds are decreased
- Normal vesicular breathing with prolonged expiration.
- Coarse crepitations at lung bases heard during inspiration and expiration both phases and change in character or disappear after coughing.
- Rhonchi at expiration.

Look features of respiratory failure and heart failures.

Features of type II respiratory failure
- Central cyanosis
- Flapping tremor
- Bounding pulse.

Features of right heart failure (Cor pulmonale)
- Raised JVP
- Right ventricular heave
- Loud P2
- Enlarged liver
- Pedal edema

BLUE BLOATERS AND PINK PUFFERS

Although chronic bronchitis and emphysema mostly occur in combination, yet the patient may present with predominant features of chronic bronchitis or emphysema.

When the chronic bronchitis is predominant with cough, sputum, cyanosis, hypercapinia, pulmonary hypertension, right ventricular failure & peripheral edema occurring at an early stage, patient is called "BLUE BLOATER"

When emphysema is pure, patient is always breathless but not cyanosed. Cough, edema & heart failure are not prominent, and the patient is termed as "PINK PUFFER". These patients are not cyanosed because hypoxia increases respiratory rate that compensates hypoxia.

Blue bloaters (chronic bronchitis prominent)	Pink Puffers (emphysema predominant)
• Major complaint is chronic cough, productive of mucopurulent sputum, with frequent exacerbations due to chest infections. • Often presents in late 30s and 40s. • Dyspnea usually mild. • Patient usually over weight. • Cyanosis is common, peripheral edema also occurs due to cor pulmonale, therefore called blue bloaters. • Rhonchi are common on auscultation.	• Major complaint is dyspnea, often severe. • Usually presenting after age 50. • Patients are usually thin, with recent weight loss common. • Patient is uncomfortable with use of accessory muscles of respiration but there is no cyanosis or peripheral edema, therefore called pink puffers. • Breath sounds are very reduced. No rhonchi.
• Hemoglobin usually elevated (15-18 g/dl) • PaO2 reduced (45-60 mmHg) • PaCO2 slightly to markedly elevated • Chest X-ray shows increased interstitial markings (dirty lungs) especially at bases. Diaphragms are not flattened.	• Hemoglobin usually normal (12-15 g/dl) • PaO2 normal to slightly reduced (65-75 mmHg). • PaCO2 normal to slightly reduced (35-40 mmHg). • Chest x-ray shows hyperinflation with flattened diaphragm. Vascular markings are diminished, particularly at the apices.
• Pulmonary function shows normal total lung capacity TLC; may be slightly increased	• TLC markedly increased.

INVESTIGATIONS

X-ray chest

X-ray chest is often normal. The classic features are signs of hyperinflation such as:

- Low flat diaphragm
- Prominent pulmonary arterial shadow at both hila.
- Narrow vertical heart (tear drop heart) due to overinflation of the lungs.
- Hypertranslucency of lung field (more blackish due to excess air in the lungs).
- Loss of peripheral vascular markings due to decreased perfusion through emphysematous area.
- Bullae may be present.

> **HYPERTRANLUSENCY OR TRANSRDIANCY**
>
> **Generalized (involving both lungs)**
> - Emphysema
>
> **Localized (involving one lung)**
> - Compensatory emphysema: when a lobe or lung is collapsed remaining normal part expands to fill the space; called Compensatory emphysema.
> - Pneumothorax
> - Reduction is chest wall soft tissues e.g. after mastectomy (removal of breast usually in breast carcinoma).
> - Air- trapping due to central obstruction: usually a complication of inhaled foreign body.

Pulmonary function tests

- Pulmonary function tests reveal obstructive lung disease:
- Forced expiratory volume in one minute FEV1 is reduced (< 80% predicted).
- Ratio of FEV to vital capacity (VC) is also decreased (< 70%).
- Peak expiratory flow PEF – reduced
- Lung volumes: Total lung capacity (TLC), residual volume (RV) and RV/TLC ratio is increased.

Arterial blood gas measurement

- Arterial blood gas pressure remains normal for a longer time in emphysema than in chronic bronchitis.
- In advanced cases there is evidence of hypoxemia and hypercapnea.

Sputum C/S

Sputum C/S is performed in acute exacerbation of COPD, and reveals streptococcal pneumoniae, H. influenzae or Moraxella catarrhalis.

ECG

- ECG may show:
- Tall P wave (P pulmonale) in case of cor- pulmonale.
- Right bundle branch block
- Signs of right ventricular hypertrophy
- Supraventricular arrhythmias such as atrial flutter or fibrillation.

Echocardiography

Performed to assess pulmonary artery pressure.

Alpha 1-antitrypsin

The normal range is 2-4g/L.

> **INVESTIGATIONS IN COPD**
> - Chest x-ray
> - ABGs
> - Pulmonary function tests
> - Sputum culture & sensitivity
> - ECG
> - Echocardiography
> - Alpha 1-antitrpsin deficiency

CLASSIFICATION AND DIAGNOSIS OF COPD

Severity	Spirometry	Symptoms
Mild	FEV1 60-79% predicted	Smoker's cough ± exertional breathlessness
Moderate	FEV1 40-59% predicted	Exertional breathlessness ± wheeze; cough ± sputum
Severe	FEV1 < 40% predicted	Breathlessness, wheeze and cough prominent; swollen legs

DIFFERENTIAL DIAGNOSIS

- Bronchial asthma
- Bronchiectasis
- Cystic fibrosis
- Mechanical obstruction of central airway

COMPLICATIONS

- Type I and Type II respiratory failure.
- Secondary polycythemia
- Spontaneous pneumothorax
- Acute bronchitis, pneumonia and other infections.
- Pulmonary hypertension and right ventricular failure (corpulmonale)

Hypoxia → pulmonary arteriolar vascoconstriction → pulmonary hypertension → right heart failure (cor pulmonale).

MANAGEMENT

Management of an ambulatory patient (in OPD)

- The most important aspect of management is to encourage smoking cessation.
- The only drug therapy that is documented to alter the natural history of COPD is supplemental oxygen in those patients with resting hypoxia.
- A trial of bronchodilators such as ipratropium bromide (Atem inhaler) or sympathomimetic (Ventolin) is advised in all patients with symptomatic COPD.
- Oral theophyline (Theograd) is a third-line agent in COPD- after ipratopium and sympathomimetic agents.
- Oral corticosteroids (Deltacortil) are frequently prescribed for patients with asthmatic bronchitis and those with frequent exacerbations or disabling symptoms who fail to respond to therapy with ipratropium, sympathomimetics and theophylline.
- Antibiotics are required to treat acute bronchitis or to treat severe exacerbations of COPD.

Stop smoking
Complete stopping of smoking & change of occupation related to dust. The nicotine trandermal patch increases cessation rates in motivated smokers who are highly dependent on nicotine. Education and behavior therapy helps the patients in stopping smoking.

Oxygen therapy

Long term domiciliary oxygen therapy (LTOT) is home oxygen therapy in low dose for prolonged period to reduce hypoxemia in COPD. Benefits of continuous oxygen therapy at home in advanced COPD include longer survival, reduced hospitalization needs, decreased pulmonary hypertension and better quality of life. Oxygen by nasal prongs must be given at least 15 hours a day at a flow rate of 1-3 L/min to a patient whose resting PaO_2 is below 55 mmHg. Edhi Foundation helps the needy patients in this regard and supplies oxygen cylinder with refilling facilities.

Ipratropium bromide (Atem inhaler)
Ipratropium bromide is superior to sympathomimetics (such as salbutamol) inhaler in achieving bronchodilation in patients with moderate to severe COPD. The combination of ipratropium and salbutamol is slightly more effective in COPD and than either agent alone. 2-4 puffs 6 hourly are recommended.

Theophylline (Theograd)
Theophylline is used in patients who fail to respond to inhaled bronchodilators or those with sleep related respiratory disturbance. Although theophylline is a mild bronchodilator in COPD patients with partial reversibility of airflow limitation, its principle value in COPD is due to improvement in respiratory muscle performance. Tab. Theograd 350 mg twice daily is recommended.

Corticosteroids
Oral corticosteroids are given as a trial for 2-4 weeks and spirometry is performed before and after therapy to document objective (spiromatic) improvement. The drug should be discontinued if the response is less than 20% of FEV1. is. Prednisolone (Tab. Deltacortil 5mg) 0.5-1 mg/kg/d is recommended. If the patient is responsive to corticosteroid and daily requirement

of predinisolone is less than 20mg, corticosteroid inhaler may be advised. However inhaled corticosteroids are not routinely used in COPD and their role to prevent deterioration in COPD is not clear.

Antibiotics

Antibiotics may be used in patients of COPD as following:

- As prophylatically in patients with frequent exacerbations of chronic bronchitis.
- To treat an acute episode of bronchitis.
- To treat severe COPD exacerbation.

Respiratory infection should be treated promptly because it aggravates breathlessness and may precipitate type II respiratory failure in patient with severe airflow obstruction. The usual organisms are Streptococcus pneumoniae or H. influenzae.

One of the following is the recommended antibiotic:

- Amoxicilline calvulanic acid (Augmantin 625 mg) 8 hourly.
- Clarithromycin (Tab. Klaricid) 250-500mg twice daily.
- Doxycycline (Cap. Vibramycin 100mg) once daily.
- Cefaclor (Cap. Ceclor 500mg) 8-hoursly.

A 5-10 day course of treatment is usually effective.

- **Other measures**
- Hot drink or steam inhalation to liquefy the sputum & to make it easier to cough up.
- Cough suppressants are contraindicated.
- Chest physiotherapy: it may aid the patient to exhale slowly and steadily and to expectorate.
- Guided aerobic physical exercise program such as walking 20 min three times weekly is helpful to prevent deterioration of physical condition.
- Influenza and pneumococcal vaccines should be given because these infections may lead to acute exacerbation of COPD.

MANAGEMENT OF ACUTE EXACERBATION OF COPD (For hospitalized patient)

- Oxygen (low dose)
- Nebulization with ipratropium or salbutamol (Ventolin) or combination of both.
- Antibiotics
- Corticosteroids i.v.
- Diuretics if there is cor pulmonale
- Chest physiotherapy
- Theophylline should not be initiated in the acute setting but if patient is already taking then continue it.
- Cardiac atrial arrhythmia usually responds to aggressive management of COPD itself.

Noninvasive positive pressure ventilation (NPPV) delivered via facemask helps in type II respiratory failure. NPPV should be used early when there is mild to moderate respiratory acidosis (pH 7..25-7.35).

Respiratory stimulant: in case of respiratory failure respiratory stimulant such as Doxapram 1.5-4.0 mg/min by slow i.v. infusion may help in the short term to arouse the patient and to stimulate coughing, with clearance of some secretions. Doxapram is used when patient is not responding to noninvasive positive pressure ventilation and endotracheal intubation is not indicated such as in significant comorbidity.

Mechanical ventilation with endotrachial intubation may be required in patients with progressive respiratory failure not responding to medical treatment and NPPV.

SURGICAL TREATMENT OF COPD

Bullectomy:

Surgical removal of giant bullae that does not participate in ventilation and perfusion and that also compresses adjacent lung tissue that has preserved function.

Lung volume reduction surgery

This is an experimental surgical approach to relief dyspnea in patients with advanced emphysema and lung hyperinflation. Bilateral resection of 20-30% of lung volume results in improvement in pulmonary function. Trial is going on and complete results are awaited.

Lung transplantation:

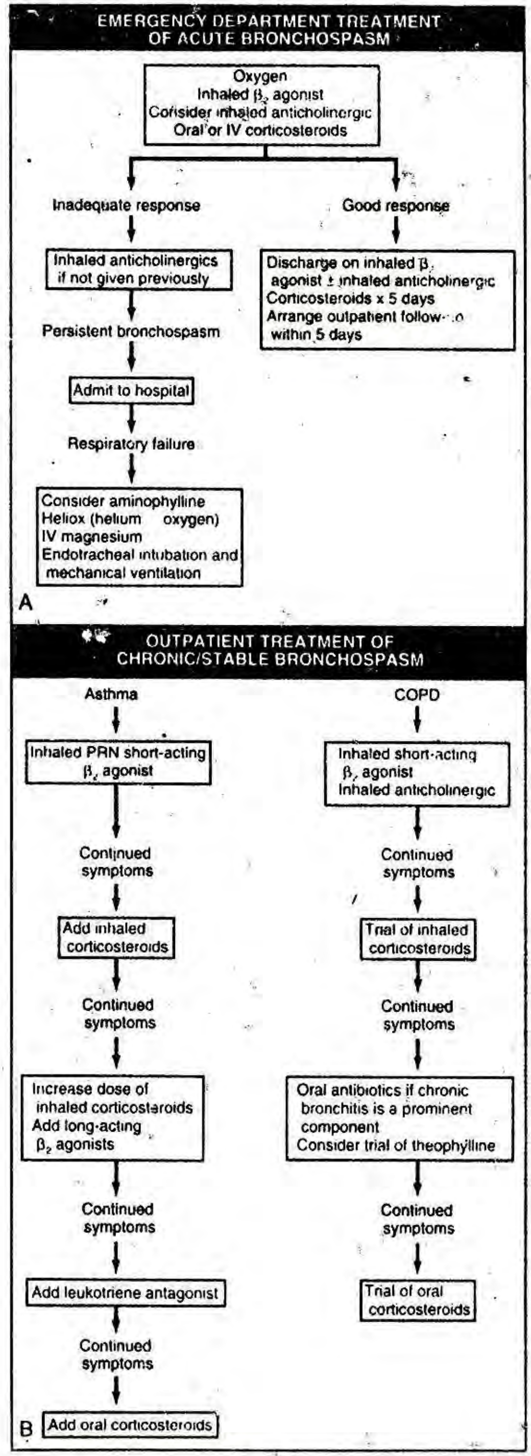
Single or both lung transplantation may be the choice in severe COPD not responding to medical treatment. Severe lung disease, limited activities of daily living, exhaustion of medical therapy and limited life expectancy without transplantation are the indications. Normal function of other organs and good social support are required. Two year survival rate after lung transplantation is 75%.

PROGNOSIS

Prognosis is poor for clinically significant COPD. The median survival time of patients with severe COPD (FEV1 < 1 L) is about 4 years. Prognosis depends on pulmonary dysfunction at the time of presentation.

AIR TRAVEL

Patients with resting PO2 in 70s require supplemental oxygen during air travel. Gross hypoxemia or hypercapnia is a relative contraindication to air travel.



LUNG TRANSPLANTATION

Indication and patient selection

Patient under 60 years with a life expectancy of less than 18 months without transplantation, no underlying malignancy and no serious systemic disease.

Following diseases are treated by lung transplantation.

- Emphysema- smoking induced or due to alpha- one antitrypsin deficiency.
- Idiopathic pulmonary fibrosis
- Cystic fibrosis
- Eisenmenger's syndrome
- Primary pulmonary hypertension

LUNG TRANSPLANTATION OPTIONS
Single lung transplantation
• Emphysema • Idiopathic pulmonary fibrosis • Primary pulmonary hypertension
Bilateral lung transplantation
• Cystic fibrosis • Emphysema • Primary pulmonary hypertension • Bronchiectasis
Living related lobar transplantation
• Cystic fibrosis • Bilateral lower lobe transplantation from two Different living donors
Heart-lung transplantation
• Congenital heart diseases with Eisenmenger's syndrome. • Concomitant left ventricular failure and end stage lung disease.

Recipient selection

Patient under 60 years with end – stage lung disease, a life expectancy of less than 18 months without transplantation, no underlying malignancy and no serious systemic disease such as coronary artery disease, renal insufficiency, liver disease, osteoporosis and chronic unresolved infection. Abstinence from smoking should be at least 6 months.

Donor selection

Age under 40 years, good cardiac and lung function and chest measurement slightly smaller than those of recipient. ABO blood group is essential.

Complications

- ***Acute rejection:*** usually in first 3 months presenting with dyspnea, fever and cough.
- ***Chronic rejection*** in the form of bronchiolitis obliterans.
- ***Infections:*** particularly within first 3 months.
- Complications of immunosuppressive therapy.
- ***Recurrence of underlying disease*** such as sarcoidosis.

Prognosis

Two-year survival of 75% and 5- year survival of almost 50%.

BRONCHIAL ASTHMA

Paroxysmal attacks of breathlessness, chest tightness and wheezing resulting from paroxysmal narrowing of the bronchial airways is called bronchial asthma. The narrowing of bronchial airway is due to muscle spasm, mucosal swelling and viscid bronchial secretions occurring as a result of inflammatory reaction within the bronchial walls. About 7% of adults and 15% of children have asthma. Genetic and environmental factors are involved. The highest incidence is in New Zealand, Australia and UK and the lowest in China and Malaysia.

TYPES

Early – onset asthma (episodic, atopic or extrinsic asthma)
Onset of this type of asthma occurs in childhood and in atopic individual i.e. who readily forms 1gE antibodies to common materials present in an environment e.g. pollen, house dust, feathers, animal dander, fungal spores and ingested allergens derived from fish, eggs, milk, yeast and wheat. Atopy runs in families.

Other allergic disorders such as allergic rhintis and eczema are often present. Family history of these disorders and of early onset asthma is common. Due to the antigen – antibody inflammatory reaction certain mediators are released which produce muscle spasm, mucosal swelling and mucus hypersecretion.

Eosinophil infiltration is a characteristic feature of asthmatic airways. These cells are capable of releasing a variety of mediators which are toxic to airway epithelium and induce inflammatory reaction.

Late onset asthma (chronic or non atopic or intrinsic asthma).
This occurs mostly in adults. External allergens play no part in the production of this type of asthma, so the term intrinsic asthma is sometime used.

Bronchial smooth muscles and bronchial secretions are controlled by autonomic nervous system. Cholinergic and alpha – adrenergic stimulation cause bronchoconstriction while the beta – adrenergic stimulation causes relaxation. It is theorized that exposure to cold, exercise, air - pollution, emotion and aspirin stimulate cholinergic and alpha – adrenergic system resulting in bronchial constriction and increased bronchial mucus secretions.

ETIOLOGY

Atopy and Allergy
The term atopy is used to describe those individuals who readily develop 1gE antibodies against common materials present in the environment. Genetic and environmental factors affect serum 1gE levels. The allergen responsible for asthma in atopic individuals generally enter the bronchi with the inspired air. The antigen – antibody reaction in the bronchi causes release of biochemical mediators from cells such as mast cells which provoke bronchial constriction and inflammatory reaction of allergic type in the bronchial wall. Eosinophils, neutrophils, alveolar macrophages and T-lymphocytes also play important role in this inflammatory reaction.

Airway Hyperactivity
The tracheobronchial tree of asthmatic individuals appears to have an exaggerated reactivity to non-specific stimuli. Although the mechanism of hyperactivity is unknown, it is suggested that the abnormality may exist in the nerves that regulate the tone of the muscle i.e. autonomic nervous system. Stimulation of parasympathetic system by non-specific irritants such as dust produces bronchial constriction. On the other side deficiency in the sympathetic system also causes hyperactivity resulting in bronchial constriction. Bronchial reactivity can be demonstrated by asking the patient to inhale histamine or methacholine (bronchial provocation tests). This induces a transient episode of airflow narrowing in susceptible individuals.

PATHOGENESIS

Inflammation and asthma

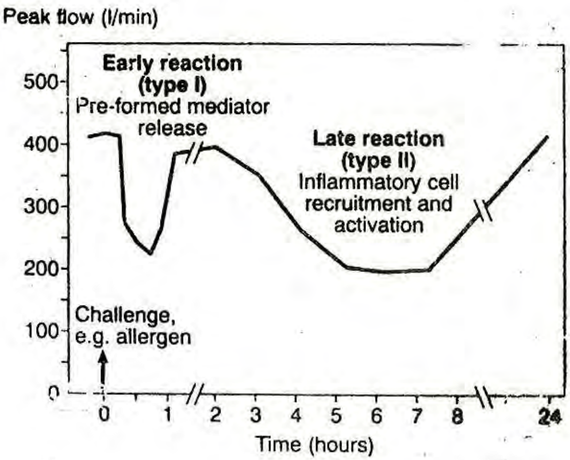
In recent years, the main role of airway inflammation in the pathophysiology of asthma has been recognized. The asthmatic inflammatory reaction has been characterized as consisting of an immediate response and a late response.

Immediate response

Inhalation of allergens initiates immediate response in the form of dyspnoea, cough, chest tightness and wheezing. This response occurs shortly after allergen exposure within the first 15 min – 1 hour. The immediate response is presumed to be caused by mediators of immediate hypersensitivity e.g. mast cells are activated leading to release of chemical mediators that produce inflammatory reaction and symptom formation.

Late phase response (or reaction)

This inflammatory phase occurs 4-6 hours later after exposure to allergens. It is thought to be caused by an influx of inflammatory cells such as eosinophils and neutorphils. These cells release chemical mediators that produce inflammation and symptom formation. It is worth noting that asthmatic patients may suffer only an immediate reaction, only a late phase reaction, or a dual reaction.



Clinical significance

Clinically these two phases of inflammation have tremendous implication because some drugs used in the treatment of asthma such as salbutamol (Ventolin) and theophylline prevent the early phase while the anti- inflammatory drugs such as corticosteroids and cromolyn sodium are effective in blocking the late phase of inflammation. The late phase responds poorly to inhalation of salbutamol.

PRECIPITATING FACTORS

- Abrupt changes in weather
- Cold air
- Dust, tobacco smoke, atmospheric pollution.
- Exercise; usually at termination of exercise.
- Respiratory viral infections
- Emotional stress.
- Drugs
  Aspirin and other non-steroidal anti inflammatory drugs.
  Beta-blockers: e.g. propranolol

PRESENTATIONS OF BRONCHIAL ASTHMA

Bronchial asthma may be either episodic o chronic. There is a tendency for atopic individuals to develop episodic, and non-atopic individuals chronic asthma.

Episodic asthma

In this form of disease the patient has no respiratory symptoms between episodes of asthma. Attacks of wheeze and dyspnoea may occur at any time and can be of sudden onset. Precipitating factors may be allergens, exercise and viral infection such as common cold. Duration of attack varies from few minutes to several days.

Chronic asthma

In this form of asthma symptoms may be chronic unless controlled by appropriate therapy. These symptoms are chest tightness, wheeze and dyspnea on exertion, together with spontaneous cough and wheeze during night. Cough productive of mucoid sputum with recurrent episode of respiratory infection is common.

Severe acute asthma (status asthmaticus)

This term describes life-threatening attacks of asthma. Acute and chronic both types may lead to status asthmaticus. It is a state of continuous or prolonged attack of asthma associated with severe

respiratory distress & arterial hypoxemia. The respiratory symptoms are accompanied by tachycardia, pulseus_ paradoxus, sweating & central cyanosis. Chest is held near the position of full inspiration. There is vesicular breathing along with expiratory and inspiratory rhonchi. In very severe asthma airflow may become so restricted that rhonchi are no longer produced and the condition is called **"silent chest".**

The patient adopts an upright position, fixing the shoulder girdle to assist accessory muscles of respiration.

CLINICAL FEATURES OF ACUTE ASTHMA

Symptoms

- Feeling of tightness in the chest.
- Episode of dyspnea.
- Unproductive cough which aggravates the dyspnea.
- Wheeze

On Examination

Mild attack

- Slight tachycardia, tachypnoea.
- Breath sounds vesicular with prlonged expiration.
- Mild diffuse wheezing (rhonchi)

Moderate attack

- Use of accessory muscles of respiration.
- Decreased breath sounds.
- Loud wheezing.
- Retraction of intercostals muscles.
- Chest hyper-resonant.

Severe Attack

- Fatigue.
- Pulses paradoxus.
- Inaudible breath sounds (silent chest) with diminished rhonchi.
- Inability to maintain lying position
- Cyanosis.

INVESTIGATION

Chest x-ray

There are no diagnostic features of asthma on the chest x-ray. During attack lungs appear hyperinflated while between episodes chest x-ray is usually normal. In long-standing chronic cases the appearance may be indistinguishable from hyperinflation caused by emphysema.

A chest x-ray should be performed in all patients with following indications:

Poor response to treatment in acute severe asthma.

To exclude pneumothorax a rare but potentially fatal complication of the pulmonary hyperinflation produced by severe airflow obstruction in asthma.

To exclude pneumonia, pneumothorax or pneumomediastinum.

Peak Expiratory Flow Rate (PEFR)

Measuring the peak expiratory flow rate (PEFR) with a simple, inexpensive device called **peak flow meter** can indicate the severity of airflow limitation. Predicted values for PEFR vary with sex, age, and height and are typically 450-650 L/min in men and 350-500 L/min in women. Values under 100-200 L/min indicate severe ventilatory dysfunction.

In asthma there is usually a marked diurnal variation in PEFR, the lowest values being recorded in the morning therefore PEFR should be measured in morning, in the middle of the day and before bed. Measurement of PEFR is helpful in long-term assessment of the patient's disease and response to treatment.

Arterial Blood Gases ABGs)

Measurement of arterial blood gas pressures (PaO2 and PaCO2) is necessary in the management of patients with severe acute asthma. Arterial blood gases may be normal during a mild attack, but respiratory alkalosis (↓ PCO2) and mild hypoxemia are usually observed in more severe cases, hypoxemia worsens and respiratory alkalosis disappears when respiratory muscle fatigue prevents hyperventilation. A "normal" or increased PCO2 may be a sign of impending respiratory failure, indicating the need for mechanical ventilation. PaO2 less than 60 mm Hg may be a sign of severe attack.

CLASSIFICATION OF SEVERITY OF ASTHMA EXACERBATIONS

	Mild	Moderate	Severe	Impending respiratory failure
Symptoms				
Breathlessness Speech	With activity Sentence	With talking Phrases	At rest Words	At rest Cannot speak
Signs				
Body position	Able to recline	Prefers sitting	Unable to recline	Unable to recline
Respiratory rate	Increased	Increased	Often > 30/min	30/min Central cyanosis
Use of accessory muscles	Usually not	Commonly	Usually	Paradoxical thoracoabdominal movement
Breath sounds	Moderate rhonchi at mid-to-end expiratory	Loud rhonchi throughout expiration	Loud inspiratory and expiratory rhonchi	Poor air entry Silent chest, no rhonchi
Heart rate (beats/min)	< 100	100-120	>120	Relative bradycardia
Pulsus paradoxus (mm Hg)	<10	10-25	Often > 25	Often absent
Mental status	May be agitated	Usually agitated	Usually agitated	Confused or drowsy
Functional assesment				
PEF (% predicted)	> 80	50-80	< 50	< 50
Oxygen saturation (%)	>95	91-95	< 91	< 91
PaO2 (mmHg)	Normal	> 60	< 60	< 60
PaCO2 (mmHg)	< 42	< 42	> 42	> 42

FEATURES OF ACUTE SEVERE ASTHMA

- Severe shortness of breath
- Cannot speak
- Cannot lie down
- Central cyanosis
- Unable to speak
- Exhaustion, confusion, reduced conscious level
- Relative bradycardia
- Unrecordable PEF
- Oxygen saturation < 01%

DIFFERENTIAL DIAGNOSIS OF ASTHMA

Following conditions may mimic bronchial asthma:

- Vocal cord paralysis
- Foreign body aspiration
- Laryngeotrachial mass
- Angioedema
- COPD
- Bronchiectasis
- Allergic bronchopulmonary mycosis
- Shurg-strauss syndrome
- Hysteria.

COMPLICATIONS

- Dehydration.
- Airway infections.
- Exhaustion
- Pneumothorax.
- Respiratory failure
- Cor pulmonale

MANAGEMENT

Prevention

- Avoid causative allergens such as house dust mite, pets, grass pollens and chemicals.
- Early treatment of chest infections.
- Discontinuance of cigarette smoking.
- Pneumococcal vaccination; yearly influenza vaccination for patients with moderate to severe asthma.
- Avoid beta-blockers because these drugs may worsen the bronchospasm.
- Avoid ACE- inhibitor drugs which may aggravate cough.
- *Hyposensitization (Vaccination):* This involves the subcutaneous injection of very small, but gradually increasing doses of extract of allergen believed to be responsible for patient's asthma. Although this mode of therapy improves symptoms, reduces medication requirement, and alleviates bronchial hypersensitivity yet it has risk of producing acute anaphylactic reaction, therefore precautions to combat reaction should be adopted such as injection adrenaline, atropine and hydrocortisone should be in hand.

Drug Treatment of asthma

Asthma medications can be divided into long-term control and quick-relief medications.

Long-term control medications are taken daily to achieve and maintain control of persistent asthma; these drugs are corticosteroids, long- acting bronchodilators and leukotriene receptor antagonists.

Quick-relief medications are taken to promote prompt reversal of acute airflow obstruction by direct relaxation of bronchial smooth muscle. These agents are intravenous corticosteroids, short-acting beta-adrenergic agonist, anti-cholinergics and aminophylline.

Many asthma medications can be administered orally or by inhalation. Inhalation of an appropriate agent offers the advantage of delivery of high concentrations of medications directly to the target organ. This result in a more rapid onset of pulmonary effects as well as less systemic effects compared with the oral administration of the same dose.

LONG TERM CONTROL MEDICATIONS

CORTICOSTEROIDS

Corticosteroids are the most potent and consistently effective anti-inflammatory agents; they reduce both acute and chronic inflammation resulting in control of asthma symptoms and prevention of asthma exacerbations.

Inhaled Corticosteroids

They are now considered as first-line maintenance therapy for patients who have regular persisting symptoms in spite of treatment with as – required β_2 – adrenergic agonists inhaler.

- Becotide inhaler is a low dose inhaled corticosteroid and contains 50mcg betamethasone per dose and is given as 2 puffs 2-4 times daily.
- Becloforte inhaler is a high dose corticosteroid and contains 250mcg betamethasone per dose and is given as 2 puffs 2-4 times daily. It is reserved for patients who have not responded to lower dose inhaled corticosteroids.

Maximum response from inhaled corticosteroid may not be observed for months.

Side effects:

- Common side- effects are oral candidiasis and hoarseness. Use of *spacer devices (Volumatic)* for inhalation and mouth rinsing after inhalation help prevent these side – effects.
- High – dose corticosteroids more than 800mcg/day may lead to systemic effects such as adrenal suppression, osteoporosis, skin thinning and catarac[t]

Oral Corticosteroids
Oral corticosteroids are necessary for those patients who are not controlled on inhaled corticosteroids. The dose should be kept as low as possible to avoid side effects. Alternate-day treatment is preferred to daily treatment.

Short course of oral corticosteroid is often required to control symptoms. Prednisolone (Tab. Deltacortil 5mg) 30-60 mg/day as a single dose given orally in the morning until 2 days after control is re-established. Tapering of dose to withdraw treatment is not necessary unless given for more than 3 weeks.

Early treatment of severe asthma attacks with adequate doses of oral corticosteroids usually relieves symptoms and prevents hospitalization. Some patients require continuing treatment with oral corticosteroids. Studies suggest that treatment with low dose of methotrexate can significantly reduce the dose of prednisolone needed to control the disease in some patients

LONG – ACTING BRONCHODILATORS

Beta-adrenergic agonists
Long – acting beta 2 – adrenergic agnosists provide bronchodilation for up to 12 hours after a single dose. However, because their onset of action is delayed, they should not be used in the treatment of acute asthma.

Salmeterol (Serevent inhaler) is indicated for long-term prevention of asthma symptoms – especially nocturnal symptoms – and the prevention of exercise induced bronchospasm.

Phosphodiestrase inhibitors
Theophylline causes a mild bronchodilation, has anti-inflammatory effect and enhances mucociliary clearance and diaphragmatic contractility.

Sustained- release theophylline preparation (Theograd 350 mg) is used as adjuvant therapy to control nocturnal symptoms in patients whose symptoms persist despite use of corticosteroid and a beta-adrenergic agonist.

Dose 200-500mg BID. Serum theophylline levels should be measured 3-5 days after therapy is started. Therapeutic level of theophylline is 10-15 mcg/ml, concentration above 20 mcg/ml is often associated with side effects.

Cimitidine, oral contraceptives, macrolides and quinolone antibiotics decrease theophylline clearance, therefore increasing its half – life while rifampicin, phenytoin, barbiturates and tobacco increase theophylline clearance leading to shortening of its half – life.

MEDIATOR INHIBITORS

Cromolyn Sodium (Intal) and Nedocromil sodium
Cromolyn Sodium (Intal) and Nedocromil sodium are important anti-inflammatory drugs that prevent activation of many inflammatory cells, particularly mast cells, eosinophils and epithelial cells. They are effective for mild persistent asthma particularly when exercise is a precipitating factor. These agents have no direct bronchodilator activity, so they are not effective in relieving acute symptoms of asthma.
Dose: 2 puffs 4-times daily or 10-15 minutes before exercise. Cromolyn is free of side effects while nedocromil can cause taste disturbance, cough, headache and pharyngitis.

Leukotrine receptor antagonists
Leukotrienes are potent biochemical mediators that contribute to airway obstruction and asthma symptoms by contracting airway smooth muscles, increasing vascular permeability and mucus secretion, attracting inflammatory cells. Leukotriene receptor antagonists are the newest class of medications for long- term control of asthma. Drugs in this class are Monteleukast, Zileuton and zafirlucast that may be considered as alternatives to low-dose inhaled corticosteroids in patients with mild persistent asthma.

- Monteleukast (Tab. Singulair 5mg &10mg) once a day at bedtime.

QUICK-RELIEF MEDICATIONS

Beta-adrenergic agonists

Salbutamol and terbutaline are the first line therapy for rapid symptomatic improvement in patients with acute bronchospasm. These agents relax airway smooth muscles and cause a prompt increase in airflow and reduction of symptoms.

Inhaled beta-adrenergic agonists

Inhaled beta-adrenergic agonist therapy is as effective as oral or parenteral therapy in improving acute asthma and offers the advantages of rapid onset of action (<5 min) and less systemic side effects such as palpitation. Therefore inhaled beta-adrenergic agonists are preferred to oral, subcutaneous and intravenous routes. The use of spacer device with metered-dose inhaler minimizes coordination between canister activation and inspiration, decreases oropharyngeal particle deposition and allows effective delivery even during tidal breathing.

Metered-dose inhaler is as effective as nebulizer if patient can inhale with coordination, however nebulizer is perceived to be more effective than metered-dose inhaler because it is given in higher doses (usually 25-30 times). Nebulizer therapy may be more effective in patients who are unable to coordinate inhalation of medication from a metered-dose inhaler because of age, agitation or severity of the exacerbation.

Inhaled beta-adrenergic agonist is preferred to oral or parenteral beta-adrenergic agonist because it is rapid and with less side effects.

Metered-dose inhaler is as effective as nebulizer if patient can inhale with coordination, however in nebulizer higher doses of drugs are used that cause more bronchodilation and there is no need of coordination therefore preferred in acute severe asthma.

Dose: Salbutamol (Ventolin inhaler) or terbutaline (Bricanyl inhaler) 2 puffs as required.

Oral Beta-Adrenergic Agonists

They are indicated only for the patients who cannot use inhaled medications. Salbutamol (Tab. Ventolin) is available in 2mg, 4mg, and given 3-4 times daily, 4mg SR (sustained Release), 8mg SR are given 3 times daily.

Systemic corticosteroids

Systemic corticosteroids are effective treatment for patients with moderate to severe exacerbations or for patients who fail to respond to inhaled beta 2-adrenergic agonist. They should be given early and in higher doses.

- Prednisolone (Tab. Deltacortil 5mg) is given as 0.5-1 mg/kg/d in one or two divided doses orally for 3-10 days.
- Hydrocortisone (Inj. Solu- Cortef 100mg, 250 mg, 500mg) is given as 2.5-4 mg/kg i.v 6 – hourly in severe acute asthma (status asthmaticus).

Anticholinergic

Ipratropium bromide (Atem inhaler & Atrovent nebulizer solution) is useful in the following conditions:

- Patients not responding to beta agonists
- Patients whose bronchospasm is secondary to bronchitis or due to beta-blocker medications.
- As an alternative in patients who cannot tolerate beta 2-adrenergic agonists.
- As an adjuvant to short acting beta 2-adrenergic agonist in moderate to severe asthma exacerbation.

Aminophylline

Intravenous aminophylline (a phosphodiesterase inhibitor) is not used as a first-line agent but may be considered for patients in status asthmaticus who do not respond to maximal inhaled bronchodilators, corticosteroids and ipratropium bromide. Aminophylline is also recommended in patients who develop paradoxical abdominal and diaphragmatic movement on inspiration that indicates diaphragmatic fatigue, aminophylline infusion is effective in improving diaphragmatic contractility.

PHARMACOLOGIC THERAPY OF ASTHMA

Long-term control medications

- Corticosteroids: inhaled or oral
- Long acting bronchodilators such as:
  Salmeterol inhaler (long acting β2- agonist)
  Theophylline (phosphodiestrase inhibitor)
  Cromolin sodium (mast-cell stabilizer)
- Monteleukast (leukotrine receptor antagonist)

Quick-relief medications

- Salbutamol: inhaler or nebulizer (short acting β2 – agonist)
- Corticosteroids: oral prednisolone or intravenous hydrocortisone.
- Ipratropium bromide inhaler (anticholinergic).
- Aminophylline infusion.

Use of an inhaler

- The canister is shaken
- The patient exhales to functional residual capacity (not residual volume), i.e. normal expiration.
- The aerosol nozzle is placed to the open mouth.
- The patient simultaneously inhales rapidly and activates the aerosol.
- Inhalation is completed.
- The breath is held for 10 seconds if possible.

Even with good technique only 15% of the contents is inhaled and 85% is deposited on the wall of the pharynx and ultimately swallowed.

Spacers

These are plastic conical spheres inserted between the patient's mouth and the inhaler. They are designed to reduce particle velocity so that less drug is deposited in the mouth. Spacers also diminish the need for coordination between aerosol activation and inhalation. They are useful in children and in the elderly.

CLINICAL APPROACH

In this section we will discuss the clinical approach for the different presentations of asthma under the following headings:

Stepwise management of chronic persistent asthma.

Management of mild asthma exacerbations.

Management of acute severe asthma (status asthmaticus).

STEPWISE MANAGEMENT OF CHRONIC PERSISTENT ASTHMA

Stepwise approach is used to treat asthma depending on the severity and frequency of attacks. The initial treatment for each patient should be chosen individually depending upon the severity of disease. It is better to start treatment which is likely to achieve disease control rapidly and then "step down" rather than to start with inadequate treatment and then have to "step up". Patient compliance is likely to be better when control of symptom is achieved rapidly.

Step 1:

Occasional use of inhaled β2- agonist

Inhaled short acting beta2 – agnosists (salbutamol, terbutaline) are used for this purpose to relieve symptoms

If patient needs inhaler more than once daily or more than three times weekly, step-2 treatment should be started.

Step-2:

Regular inhaled anti-inflammatory agents

Inhaled short-acting β2 –agonists are used as required Plus

Inhaled steroids (beclomethasone, budesonide) should be prescribed up to 800μg daily.

Step-3:

High dose inhaled corticosteroids, or low dose inhaled corticosteroids plus long-acting inhaled β2- agonist

Inhaled short-acting β_2- agonist are used as required plus High dose inhaled corticosteroids 800-2000μg daily OR.

Low dose inhaled corticosteroids 800μg daily plus long acting inhaled β2- agonist such as salmeterol 50 μg 12-hourly or oral theophylline is added.

Step-4:

High dose inhaled corticosteroids and regular bronchdilator

Inhaled short- acting β_2 – agonist are used as required plus inhaled high dose corticosteroids 800- 2000 µg daily plus a trial of one or more of the following:

- Inhaled long acting beta2 – agonist (salmeterol).
- Sustained release oral theophylline
- Inhaled ipratropium bromide
- Leukotriene receptor antagonist e.g. monteleukast sodium.
- Long – acting oral beta2- agonist such as salbutamol (Ventolin SR).
- Sodium cromoglycate

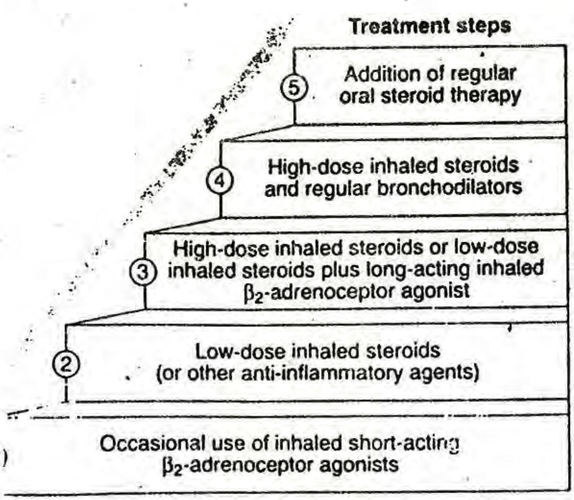
Step – 5:

Addition of regular oral cortieosteroids

Step-4 ned with regular prednisolone tablets in smallest possible single daily dose in the morning to control symptoms.

Antibiotics:

There is no evidence that antibiotics are helpful in the routine management of patients who suffer from properly diagnosed acute or chronic asthma.



Concept of step-up

MANAGEMENT OF MILD ASTHMA EXACERBATION

Inhaled short-acting beta2- agonist such as Ventolin inhaler that may be required every 3-4 hours for 24-48 hours.

If patient is already taking an inhaled corticosteroid, double the dose until improvement in peak flow.

A course of oral steroids may be necessary if symptoms persist after doubling the dose of inhaled corticosteroid.

ASSESSMENT & MANAGEMENT OF ACUTE SEVERE ASTHMA (STATUS ASHMATICUS)

It is the condition of severe and continuous bronchoplasm that has not been controlled by the patient's use of medications.

Symptoms

History of progressively worsening dyspnea, cough, tachypnea, chest tightness and wheezing over a period of hours to days.

The patient is generally sitting forward and may be unable to complete a sentence in one breath or unable to speak because of severe dyspnea.

Physical examination

- Use of respiratory muscles
- Tachycardia – pulse > 110 beats/min
- Tachypnea – respiratory rate > 25/min
- Pulsus paradoxus (decrease in systolic B.P> 10 mm Hg during inspiration).
- Paradoxic abdominal and diaphragmatic movement on inspiration indicates diaphragmatic fatigue.
- Wheezing: if the wheezing is decreased or absent " silent chest " it indicates worsening obstruction.
- Mental status changes (confusion): these are secondary to hypoxia and hypercapnia and constitute an indication for urgent intubation.

Investigations

1: *Peak Expiratory Flow Rate (PEFR)*

- It should be recorded immediately.
- In previously fit asthmatics reading of < 200 liters / min is indicative of severe asthma and values of < 100 liters / min must be taken as evidence of life threatening episode.

2. *Arterial Blood Gases*

- Mild: Decreased PO_2 & PCO_2, increased pH.
- Moderate: Decreased PO_2, normal PCO_2, normal pH.
- Severe: Markedly decreased PO_2, increased PCO_2 and decreased pH.

Blood Picture: shows leukocytosis in case of bacterial infection.

Chest X-Ray: Features of hyperinflation e.g. flattening of diaphragm, look for pneumonic patch and pneumothorax.

Treatment

1. Oxygen

High concentration of oxygen (40-60%) is used and set at a high flow rate to treat hypoxemia. High conc. oxygen therapy does not cause or aggravate CO_2 retention in asthma (as it may cause in COPD).

It is generally started at 2-4 lit / min via nasal canulla or ventimask, further adjustment are made according to the ABGs.

Monitoring with pulse oximeter is necessary, keep oxygen saturation above 90% and $PO_2 > 60$ mmHg.

2. *Inhaled beta-2 Agonist:*

An inhaled beta-2 agonist drug such as salbutamol (Ventolin solution) 2.5-5 mg (0.5 – 1 ml) diluted in 3 ml of normal saline mixed with oxygen should be given by nebulizer.

Upto three nebulizer treatment may be given over 60-90 minutes using peak expiratory flow rate (PEFR) as a guide.

3. *Systemic corticosteroids*

Systemic Steroids are necessary for the treatment of all cases of severe acute asthma. Hydrocortisone (Inj. Solu- Cortef) 200 mg 4 hourly IV should be administered for the first 24 hours and continue if the patient is seriously ill. If the patient is stable, systemic steroid treatment with oral prednisoione 30-60 mg daily is recommended for 2 weeks.

If the patient fails to respond to the above treatment following measures can be done.

- Epinephrine (1:1000 conc.) 0.3 – 0.5 ml subcutaneously, may be repeated after 15 – 20 minutes.
- Ipratropium bromide (Atrovent) 0.5 mg mixed with the beta agonist in nebulizer 6 hourly until there is clinical response.
- If there is no response one of the following infusion is given:

  Aminophyline 250 mg IV over 20 minutes.
  OR
  Salbutamol IV 3-20μg/min.

Note:

Aminophylline IV is not used as a first time drug for severe asthma, because of its narrow therapeutic index. Frequent monitoring of blood levels is required to prevent toxicity. It is used in those patients who do not respond to maximal inhaled bronchodilators.

4. Antibiotics

The routine use of antibiotic therapy for acute or chronic asthma is not recommended. If there is fever, purulent sputum, leukocytosis and infiltrate on X-ray chest suggesting infection antibiotic is added such as Inj. Augmantin 1.2 g i.v. 8 hourly.

5. Assisted Ventilation

Mechanical ventilation is necessary as a life saving procedure in a few patients. Following are the indications for endotracheal intubation and assisted ventilation:

- Coma
- Exhausion, confusion, drowsiness
- Deterioration of ABGs despite optimal therapy such as severe hyhpoxemia, carbon dioxide retention and acidosis.

6. Recovery

Recovery is gradual. Sudden cessation of therapy often leads to recurrence of severe asthma, hence treatment should never be discontinued or reduced abruptly. Nebulizer therapy should be gradually tapered, and replaced with metered dose inhaler, oral prednisolone should replace IV hydrocortisone and then should be continued for 2 weeks. Follow up after discharge from hospital is important.

DIFFERENCE BETWEEN BRONCHIAL AND CARDIAC ASTHMA

A large number of patients being treated for shortness of breath considering respiratory system involvement are found to be having cardiac problems in the form of left ventricular dysfunction, congenital heart disease, valvular or pericardial diseases. Therefore proper history, examination and investigations are required.

FEATURES	BRONCHIAL ASTHMA	CARDIAC ASTHMA (Left ventricular failure)
Definition	Characterized by episodes of dyspnea accompanied by wheezing resulting from temporary narrowing of the bronchi by muscular spasm and mucus secretion.	Characterized by episode of dyspnea, which may or may not be accompanied by wheezing occurring in association with pulmonary congestion or edema.
History	History of previous periodic attacks of asthma. Family history of allergic diseases such as eczema, rhinitis or urticaria.	Presence of cardiac risk factors such as diabetes, hypertension, smoking and family history. Previous history of angina, myocardial infarction or valvular heart disease
Time of onset	Usually in early morning	Usually in the middle of the night due to orthopnea and paroxysmal nocturnal dyspnea
Symptoms	Dyspnea and cough with expectoration of small sticky sputum.	Dyspnea and cough with expectoration of watery and frothy secretions which may be blood stained
Signs	• Chest may be barrel shaped – only expiration is prolonged • Rhonchi more prominent than crepitations and are heard diffusely all over the lung. • No cardiomegaly except in advanced stages when there is right ventricular failure due to pulmonary hypertension (corpulmonale)	• Chest may be normal in shape • Inspiration & expiration both are prolonged • Crepitations more prominent than rhonchi and are heard at the bases initially • Cardiomegaly with heaving of apex beat may be detected. • Raised JVP, pedal edema may present • Gallop rhythm may be present • Murmurs may be present
Chest x-ray	Normal or hyperinflation	Cardiomegaly with prominent pulmonary artery shadow
ECG	ECG may show sinus tachycardia P – pulmonale and features of right ventricular hypertrophy may present	ECG may show left ventricular hypertrophy, left atrial hypertrophy myocardial infarction
Echocardiography	Normal or enlarged RV	Systolic or diastolic dysfunction or congenital and valvular lesion
Pulmonary function test	Obstructive pattern	
Response to Treatment:	Responds best to bronchdilators	Responds best to diuretics, nitrates, ACE inhibitors according to situation

SLEEP APNEA/ HYPOPNEA SYNDROME

This syndrome is characterized by recurrent upper airway obstruction during sleep when loss of normal pharyngeal tone allows the pharynx to collapse passively during inspiration.

Etiology

- Male gender
- Obesity
- Tonsillar hypertrophy
- Nasal obstruction
- Hypothyroidism and acromegaly
- Ingestion of alcohol or sedatives before sleep

Clinical features

- If narrowing is slight, it leads to snoring. If upper airway narrowing progresses to the point of occlusion or near occlusion, sleeping person increase respiratory effort to try to breathe until the increased effort transiently awaken him. This recurrent cycle of apnea, awakening, apnea, awakening may repeat itself many hundreds of times per night.
- Patient complains of day – time sleepiness, he feels he has been asleep all night but wakes unfreshed.
- Bed partner reports loud snoring and often have noticed multiple breathing pauses (apnea).
- Patient also complains of difficulty in concentration, impaired cognitive function, impaired memory and work performance, depression, loss of libido, irritability and nocturia.
- Hypertension and ischemic heart disease are also complications.

Examination

- Nasal obstruction
- Narrow oropharynx due to excessive soft tissue folds, large tonsils or prominent tongue.
- Features of pulmonary hypertension or cor pulmonale may be present.

Investigations

Polysomnography: this is the overnight study of breathing, oxygenation (oxygen saturation) and sleep quality. It shows apnea episodes as long as 60 seconds, oxygen saturation falls often to very low level and brady or tachy arrhythmias.

Treatment

- Weight loss
- Strict avoidance of alcohol and hypnotic medications.
- Nasal continuous positive airway pressure (nasal CPAP) is curative in many patients.
- Treatment of curable conditions such as deviated nasal septum.
- *Uvulopalatopharyngoplasty* : a procedure consisting of resection of pharyngeal soft tissue and amputaion of approximately 15 mm of free edge of the free edge of the soft palate and uvula is helpful in about 50% of cases.

HYPERVENTILATION SYNDROME

This syndrome is characterized by increase in alveolar ventilation that leads to hypocapnea.

Central neurogenic hyperventilation occurs in brain stem injury presenting with sustained pattern of rapid and deep breathing.

Causes of hyperventilation may be organic or functional.

Organic causes
Organic causes are pregnancy, hypoxemia, obstructive and infiltrative lung diseases, sepsis hepatic dysfunction, fever and pain

Functional hyperventilation
Functional hyperventilation may be acute or chronic, usually due to anxiety.

- In acute form patient (usually young females) present with rapid breathing, paresthesias, carpopedal spasm, tetany (due to unionization of calcium), chest pain or discomfort, choking sensation, sweating and anxiety.
- In chronic form patient presents with fatigue, dyspnea, anxiety, palpitation and dizziness.

Diagnosis

- Rule out organic causes.
- ABGs show low PCO2 and increased pH.
- Provocation test: voluntary over breathing for 2-3 min provokes similar symptoms.

Management

Re-breathing into a closed paper bag to increase CO_2.

Explanation and reassurance.

Experience sharing

Hyperventilation syndrome is a common emergency but diagnosis is late if emergency doctor is not much experienced. Chest pain, shortness of breath and twitching of hands due tetany are usual presentations. Consider possible organic causes such as sepsis and poisoning etc. and do not give oxygen. Perform ABGs and ask the attendant to bring a paper bag and ask the patient to rebreath in this bag, gradually carbon dioxide increases in blood, tetany disappears and patient feels better.

HYPOVENTILATION SYNDROME

(Pickwickian syndrome)

This is an obesity related disorder in which obese individuals present with features of alveolar hypoventilation as a result of decreased ventilatory drive and increased mechanical load imposed upon the chest by obesity. Voluntary hyperventilation returns PO_2 and PCO_2 towards normal values. Most of the patients also suffer from sleep apnea syndrome.

Treatment is weight reduction, non- invasive positive pressure ventilation is helpful in some cases. Respiratory stimulant such as theophylline may be helpful.

BRONCHIECTASIS

Bronchiectasis is a condition characterized by chronic permanent dilation & destruction of bronchi due to destructive changes in the elastic and muscular layers of bronchial walls that may be diffuse or localized resulting in impairment of the drainage of bronchial secretions. Accumulation of secretions leads to persistent infection in the affected segment or lobe. Primarily it is a disorder of childhood and young adulthood but can occur at any age. In Pakistan pulmonary tuberculosis is the major cause of bronchiectasis.

ETIOLOGY

In adults (acquired in adults)

- Chronic pulmonary tuberculosis
- Suppurative pneumonia
- Lung abscess
- Aspiration pneumonia
- Allergic bronchopulmonary aspergillosis.
- Endobronchial obstruction due to tuberculosis or bronchial tumors.
- Immunodeficiency states e.g. AIDS leading to chronic respiratory infections.
- Rheumatoid arthritis, ulcerative colitis (rarely).

In Children (acquired in children)

- Secondary to pneumonia which occurs often as a complication of whooping cough and measles. Suppurative pneumonias caused by staphyloccus, klebsiella and anaerobes are common causes of bronchiectasis. Adenovirus and influenza virus may be the cause.
- Bronchial distension resulting from the accumulation of pus beyond the lesion lymphadenopathy in primary tuberculosis.
- Alpha 1- antitrypsin deficiency

Congenital

- Cystic fibrosis
- Primary hypogammaglobinemia leading to recurrent infection.
- Ciliary dysfunction syndrome
  Immotile cilia syndrome
  Young's syndrome
  Kartagener's syndrome: It is an inherited abnormality of cilia resulting in impaired airway clearance and comprises of bronchiectasis, sinusitis, infertility and transposition of viscera (situs inversus).

Organisms involved
- Bacteria: pseudomonas, H. influenzae, staphylococcus aureus, klebsiella, mycoplasma, anaerobes.
- Fungal infection
- Viruses: adenovirus, influenza virus

CLINICAL FEATURES

Symptoms

- ***Cough:*** Chronic productive cough usually worse in morning & often brought on by change of posture. Cough occurs due to accumulation of pus in dilated bronchi.
- ***Sputum:*** Copious & purulent.
- ***Fever:*** Fever with increased cough & sputum develops when spread of infection causes pneumonia which is associated with pleurisy.
- ***Hemoptysis:*** Slight to massive and recurrent hemoptysis usually associated with purulent sputum. Hemoptysis may be the only symptom of bronchiectasis and such condition is called dry bronchiectasis.
- ***General health*** deteriorates when disease is extensive with the features of weight loss, anorexia, clubbing of fingers.

On Examination

Physical signs may be unilateral or bilateral. If the bronchiectatic airways do not contain secretions there are no abnormal signs.

In the presence of large amounts of secretions numerous coarse crepitations will be heard over the affected areas, most commonly at the lung bases.

There may be signs of bronchitis, fibrosis, consolidation, collapse or cavitation.

Clubbing in severe disease.

INVESTIGATIONS

Sputum for

- Culture & Sensitivity
- AFB (Acid Fast Bacilli)

X-ray chest

Cystic bronchiectatic spaces may be visible in gross bronchiectasis at the base of lungs (honeycomb appearance in advanced cases). In mild bronchiectasis x-ray may be normal and diagnosis requiring CT scan.

High-resolution CT scanning

Bronchiectatic cavities may not be apparent on x-ray mild to moderate cases; therefore high resolution CT scan is the diagnostic study of choice. CT shows dilated bronchi with wall thickening crowded together in parallel> when seen longitudinally the airways appear as "tram tracks" and when seen in cross section they produce " ring shadow".

Bronchoscopy

Bronchoscopy is sometimes required to evaluate cause of hemoptysis, to remove retained secretions and to rule out obstructive airway lesion.

Pulmonary function tests (PFTs)

PFTs show obstructive pattern due to diffuse bronchiectasis or associated COPD.

COMPLICATIONS

- Recurrent pneumonia, lung abscess, hemoptysis.
- Pleurisy, pleural effusion or empyema.
- Clubbing
- Cor-pulmonale
- Amyloidosis (may present as nephrotic syndrome).

MANAGEMENT

Postural Drainage:

The purpose of this measure is to keep the dilated bronchi emptied of secretions.

Method:

Adaptation of a position in which the lobe to be detrained is upper most thereby allowing secretion in the dilated bronchi to gravitate towards the trachea, from which they can readily be cleared by vigorous coughing.

Percussion of the chest wall with cupped hand (chest physiotherapy) aids in dislodgment of sputum.

Antibiotic therapy

Antibiotics are given according to culture sensitivity report; meanwhile following antibiotics may be prescribed as an empirical therapy till the report is available.

- In mild cases: Amoxicillin 500 mg three times daily or Augmentin 625 mg 8-hourly.
- In moderate – severe cases:
  Inj. Augmentin 1.2 g IV 8-hourly PLUS either ciprofloxacin (Ciproxin) 250-750 mg twice daily usually for 5-10 days or Ceftazidime (Fortum) 1g I.V. 8 hourly. Inhaled aminoglycosides may be given.

Bronchodilators
Bronchdilators such as Ventolin are effective to improve obstruction and aid in clearance of secretions.

Surgical treatment
When bronchiectasis is unilateral, confined to a single lobe or segment and patient is not responding to adequate medical treatment, surgical resection of involved region should be considered. There is no role of surgery when bronchiectasis is progressive in nature such as in cystic fibrosis.

PREVENTION

Adequate treatment of whooping cough, measles and primary tuberculosis during childhood.
Early recognition and treatment of bronchial obstruction.

CYSTIC FIBROSIS

Cystic fibrosis is the most severe autosomal recessive disease as a result of mutations affecting a gene located on the *long arm* of chromosome 7 which encode for the chloride channel which is essential for regulation of salt and water movement across the cell membrane. Mostly affected patients belong to white young population of North Europe and America.

PATHOGENESIS

- The genetic defect causes an increased sodium chloride content in sweat resulting in much increased viscosity of secretions that leads to production of abnormal mucus by exocrine glands. This viscous mucus obstructs glands and ducts which ultimately causes glandular dilatation and damage to the tissue.
- In respiratory tract inadequate hydration of tracheobronchial epithelium impairs mucociliary function. Ciliary dysfunction and chronic bronchial infection leads to bronchiectasis involving gradually all areas of both lungs. *Bronchiectasis* usually develops at young age.
- There are also disorders in the gut epithelium, pancreas and liver causing malabsorption, diabetes and liver cirrhosis.
- Most men with cystic fibrosis are *infertile* due to failure of development of vas deferens.
- Early diagnosis can be achieved by neonatal screening and aminocentesis.

CLINICAL FEATURES

Respiratory effects

- Recurrent bronchopulmonary infection especially bronchiectasis presenting with cough with sputum, decreased exercise tolerance and hemoptysis.
- Sinusitis presents as facial pain and purulent nasal discharge.
- Clubbing is also present due to presence of pus in the lung.
- Older children may develop nasal polyps.
- Spontaneous pneumothorax may occur.
- Cor pulmonale and respiratory failure eventually develop.

Gastrointestinal features

- Pancreatic dysfunction leads to steatorrhea in more than 85% of patients. Small intestinal obstruction due to meconium ileus equivalent.
- Cholesterol gallstone occur with increased frequency.
- Cirrhosis of liver develops in about 5% of patients.
- There is also increased incidence of peptic ulceration and GI malignancy.

Other effects

- Malnutrition and malabsorption leads to increased pulmonary sepsis.
- Puberty and skeletal maturity are delayed. Males are almost always infertile due to failure of development of vas deferens and epididymis. Females are able to conceive but often develop secondary amenorrhea as the disease progresses.
- Joint disease and diabetes mellitus also occur.

COMPLICATIONS OF CYSTIC FIBROSIS	
Respiratory Hemoptysis Nasal polyps Spontaneous pneumothorax Cor pulmonale Respiratory failure	**Gastrointestinal** Malabsorption Intestinal obstruction Biliary cirrhosis Cholesterol gallstones
Others Diabetes mellitus (11% of adults) Delayed puberty Male infertility Arthropathy Amyloidosis Psychosocial problems	

DIAGNOSIS

Sweat test: the quantitative pilocarpine intophoresis sweat reveals elevated sodium and chloride level > 60 meq/L; however normal test does not rule out cystic fibrosis.

Family history of the disease.

Blood DNA analysis for gene defect.

Absent vas deferens and epididymis.

MANAGEMENT

- **Postural drainage** and chest physiotherapy for clearance of lower airway secretions.
- **Inhaled recombinant human Dnase**: to reduce sputum viscosity.
- **Antibiotics**: for infection. Common organisms are staph. aureus, H. influenzae, Burkholderia cepacia and pseudomonas. Some antibiotics may be given by inhalation such as tobramycin.
- **Inhaled bronchodilators:** such as salbutamol (Ventolin).
- **Inhaled corticosteroids:** to reduce inflammation.
- **Vaccination**: for pneomococcal infection and annual influenza vaccination.
- **Lung transplantation:** the only definite treatment in the form of double – lung or heart- lung transplantation.
- **Genetic screening** of family members.

PNEUMONIA

Pneumonia may be defined as an inflammation of lungs caused by acute infection and is characterized by recently developed signs of consolidation both clinically and radiologically.

TYPES

1. Community – Acquired (primary) pneumonia (typical or atypical pneumonia)
2. Hospital – Acquired (nosocomial) pneumonia
3. Aspiration pneumonia
4. Pneumonia in the immunocompromised host including AIDS.

COMMUNITY – ACQUIRED PNEUMONIA

It occurs in previously healthy individual. Normal pulmonary defense mechanisms prevent the development of lower respiratory tract infection. Community – acquired pneumonias occur when (i) there is defect in normal host defense mechanisms (ii) there is a large infectious inoculum (iii) highly virulent pathogen defeats immunity. Presentation may be **typical or atypical.**

FREQUENCY OF PATHOGENS IN PNEUMONIA

Infecting agent	Frequency %
Bacterial	
Streptococcus pneumoniae	50
Mycoplasma pneumoniae	6
Haemophilus influenza	5
Chlamydia pneumoniae	5
Chlamydia psittaci	3
Legionella pneumophilia	2
Staphlococcus aureus	2
Coxiella burnetti	1
Gram-negative bacilli	<1
Anaerobes	<1
Mycobacterium tuberculosis (an important cause of pneumonia in countries where tuberculosis is common just like Indo-Pak.	Data not available.
Viral Influenza, parainfluenza, respiratory syncytial virus and measles virus.	20
Note isolated	

Depending upon the causative organisms, rapidly of onset, clinical and radiographic evaluation and laboratory findings, this community – acquired pneumonia can be divided into typical and atypical pneumonia. This designation of "Typical" & "Atypical" is very helpful in providing clues to the possible causes.

COMPARISON OF TYPICAL AND ATYPICAL PNEUMONIA

Features	Typical pneumonia	Atypical pneumonia
Onset	Streptococcus pneumoniare (most common cause of pneumonia) H. influenzae	• Mycoplasma pneumoniae • Legionella pneuomophilia • Chlamydia pneumoniae • Viral pneumonia • Coxilla burnetti • Streptococcus pneumoniae
Clinical features	Fever, shaking chills and predominant pulmonary features such as productive cough with purulent sputum, chest pain, and signs of consolidation such as decreased chest movements, dullness on percussion, increased vocal fremitus, egophony, bronchial breath sounds and crepitations.	• Non- pulmonary features are predominant such as gradual onset of fever and dry cough. Myalgia, arthralgia, headache, sore throat, nausea, vomiting and diarrhea are predominant. • Respiratory symptoms (chest pain, productive cough) are less marked as compared to the typical pneumonia. • Abnormal chest x-ray despite minimal signs of pulmonary involvement on physical examination.
Labs	Leukocytosis	No leukocytosis
Chest x- ray	Patchy or lobar infiltrate (opacity)	Patchy non- lobar infiltrates

TYPICAL PNEUMONIA

Typical pneumonia is caused by streptococcal pneumoniae and less commonly by H. influenza. Patient presents with fever and typical respiratory features such as cough with rusty sputum and pleuritic chest pain.

CLINICAL FEATURES

Onset often sudden although sometimes it follows a minor respiratory infection of a few days duration.

Symptoms

General symptoms of infection

- Fever, temperature rises in a few hours to 39-40 C associated with chills and rigors.
- Headache, aching pains in the body and limbs.
- Vomiting
- Confusion and disorientation in the elderly

Pulmonary symptoms

Dyspnea, cough – dry at first but one or two days later it becomes productive with rusty-colored or blood-stained sputum.

Pleural symptom

Localized pain of pleural type in the chest wall at the site of inflammation that aggravates by coughing, deep breathing or movement.

On examination

General

Patient appears ill with rapid pulse rapid respiration, high fever, flushed dry skin and herpes labialis (herpes develop 1 – 2 day after fever)

Pulmonary signs

1. *Within 24 hours*
- Decreased respiratory movements.
- Slight impairment of percussion note
- Pleural rub on affected side

2. *On 2nd or 3rd day : signs of consolidation appear.*
- Decreased movement of affected side of chest.
- Increased vocal fremitus
- Dull note over consolidated area.
- Bronchial or absent breath sounds
- Increased vocal resonance
- Fine crepitations.

Resolution phase

In resolution phase most of the signs disappear by the end of second week. When resolution begins numerous coarse crepitations are heard indicating liquefaction of alveolar exudates.

DIFFERENTIAL DIAGNOSIS

- Upper respiratory tract infection
- Pulmonary tuberculosis
- Congestive cardiac failure/pulmonary edema
- Inflammatory conditions below the diaphragm such as cholecystitis, perforated peptic ulcer, pancreatitis, and liver abscess may be mistaken for lower lobe pneumonia associated with diaphragmatic pleurisy.
- Lung cancer
- Pulmonary eosinophilia, acute allergic alveolitis
- Pulmonary embolism
- Bronchiolitis oblitrans

INVESTIGATIONS

Sputum Examination

<u>*Gram staining*</u>

It may give an immediate indication of possible pathogen and thus aids in the selection of initial antibiotic treatment. Sensitivity is 62% and specificity 85% in identifying S. pneumoniae in properly collected sputum specimen.

<u>Note:</u>

An expectorated sample is often inadequate due to contamination from oral flora. Therefore a specimen may be considered adequate if the gram stain shows more than 25 neutrophils and less than 10 epithelial cells per low-power field. Specimen containing less than 25 neutrophils and more than 5 epithelial cells represent oral rather than pulmonary secretions.

<u>*Sputum culture & sensitivity*</u>

Culture is performed to identify the sensitivity and resistance of bacteria to the particular antibiotics. Sputum culture is not necessary for patients who do not require hospitalization and empirical antibiotic therapy can be started on the basis of clinical and epidemiological evidence alone.

Chest x-ray

- This is necessary for confirmation of diagnosis and for early detection of complications e.g. pleural effusion and empyema.
- Radiological changes lag behind the clinical course so that x-ray changes may be minimal at the start of illness. Usually radiological changes appear 12-18 hours after the onset of illness. Conversely, consolidation may remain on the chest x-ray for several weeks after the patient is clinically cured. However chest x -ray should always return to normal by 6 weeks. Persistent changes on chest x-ray after this time suggest a bronchial abnormality, usually a carcinoma, with persisting secondary pneumonia.
- X-ray chest may show patchy or homogenous opacity localized to the affected lobe or segment. However pattern of radiographic abnormalities is not specific to any particular cause of pneumonia.

Blood CP/ESR

WBC count is greater than 15000 per cubic meter (> 90% neutrophils) and ESR > 100 mm in first hour in streptococcal pneumonia.

WBC count is not raised in atypical pneumonia and severe bacterial infection.

Blood Culture

It should be performed in patients with severe pneumonia before starting antibiotics. It is positive in 20-25% of patients with pneumonia caused by S. pneumoniae.

Serological tests

- *Pneumococcal antigen test.* Serologic test of sputum, urine and serum for pneumoccal antigen is 3-4 times more sensitive than sputum or blood cultures.
- Serological tests (for atypical pneumonia) may be helpful in the diagnosis of mycoplasma, Legionella, chlamydia and viral infection. A four-fold rise of antibody titer suggests recent infection. Direct fluorescent antibody stain for Legionella and viruses Serology-Legionella antigen in urine. Cold aggulutinins – positive in 50% of patients with mycoplasma

Arterial blood gas measurement

Measured in seriously ill patient.

CRITERIA FOR HOSPITALIZATION OF PATIENTS WITH PNEUMONIA

- Elderly patient (> 65 years of age)
- Significant co- morbidity such as kidney, heart or lung disease; diabetes, neoplasm, immunosuppression.
- Leukopenia (< 5000 WBC) not attributable to known condition.
- Staphylococcus aureus, gram negative bacilli, or anaerobes as the suspected cause of pneumonia.
- Suppurative complications e.g. empyema, arthritis, meningitis, endocarditis.
- Failure of outpatient management.
- Inability to take oral medication.

Severe pneumonia manifests as

- Tachypnea (> 30/min)
- Tachycardia (> 140/min)
- Hypotension (< 90 mmHg systolic)
- Hypoxemia (Po_2 < 60 mmHg systolic)
- Acute alteration of mental status

MANAGEMENT

GENERAL MEASURES

Analgesics for pleural pain

Inj. Pethidine 50-100 mg OR
Inj. Morphine 10-15 mg.
NASAIDs e.g. Tab. Dolobid IBD or Tab. Ponstan Forte TDS.

Oxygen: for all hypoxemic patients to maintain PO_2 more than 60 mmHg.

Fluid: Oral or parental fluid to correct dehydration because fever and high respiratory rate can cause dehydration.

Cough Suppressant: Cough should normally be encouraged, but if it is unproductive and distressing, cough syrup containing codeine can be given such as Syp. PHOLCODINE 2tsf 3-times daily.

ANTIBIOTICS

Initially antibiotics are given empirically then can be changed according to the blood or sputum culture and sensitivity reports and serology.

Empiric antimicrobial therapy for community – acquired pneumonia

Initial therapy of pneumonia is often empirical and is based on clinical, radiographic and laboratory evaluation, severity of illness, age of patient, need for hospitalization and the presence of co-existing illness. This can be adjusted accordingly if specific etiologic agent is subsequently identified.

Treatment of outpatients

One of the following options:

- Clarithromycin (Tab. Klaricid 500mg) 12-hourly after meals.
- Azithromycin (cap. Azomax 250mg) 500mg first dose then 250mg once a day for 4 days one hour before meals.
- Erythromycin (Tab. Erythrocin 500mg) 6- hourly.
- Levofloxacin (Tab. Cravit 500mg) once a day.
- Doxycycline (Cap. Vibramycin 100mg) 12-hourly.
- Amoxicillin plus clavulanic acid (Tab. Augmentin 625 mg 8-hourly).
- Cefuroxime axetil (Tab. Zinnat 250mg) 1-2 tab. 12- hourly.

The author prefers to start treatment with Augmentin or Cravit.

Duration of treatment

- Typical pneumonia 7-10 days.
- Atypical 2-3 weeks.

Treatment of hospitalized patients

Option 1

Amoxicillin-clavulanic acid (Inj. Augmentin) 1.2 g i.v 8-hourly.

Plus

Clarithromycin Inj. Klaricid 500mg) 12 hourly.

Option 2

Ceftriaxone (Inj. Rocephin) 1-2g i.v. once daily

Plus

Clarithromycin (Inj. Klaricid 500mg) 12 hourly.

Option 3

Ceftriaxone (Inj. Rocehin) 1-2g i.v. once daily

Plus

Levofloxacin (Inj. Cravit) 12-hourly.

Option 4

Cefuroxime (Inj. Zinacef) 1.5 g 12-hourly

Plus

Clarithromycin (Inj. Klaricid) 500 mg 12-hourly.

Option 5

Levofloxacin (Inj. Cravit) 12-hourly Plus Amoxicilline- calvulanic acid (Inj. Augmentin) 1.2g i.v & hourly.

FEATURES ASSOCIATED WITH A HIGH MORTALITY IN PNEUMONIA

Clinical

- Age 60 years or older
- Respiratory rate > 30/min
- Diastolic blood pressure 60 mmHg or less
- More than 1 lobe involved on chest radiograph
- Presence of other disease (co- morbidity)
- Mental confusion.

Laboratory

- Hypoxemia (PaO_2 < 60 mmHg)
- Leukopenia (WBC < 5000)
- Leukocytosis (WBC > 20,000)
- Raised serum urea
- Positive blood culture
- Hypoalbuminemia (< 3.5g/dl)

PNEUMONIA ACCORDING TO THE ORGANISMS

STREPTOCOCCUS NEUMONIAE (PNEUMOCOCCUS)

- Most common cause of pneumonia in community. Already discussed in detail in previous section of community acquired pneumonia.
- Most frequently in children and old adult person
- The highest incidence in winter, mode of spread is by droplet infection.

Predisposing factors
- Splenectomy
- Sickle cell disease
- Viral respiratory infection e.g. influenza virus.
- COPD, CHF.
- Cigarette smoking
- Immunosuppression e.g. AIDS.
- Renal failure.

Clinical features
Onset often sudden although sometimes it follows an influenza virus infection.

Symptoms
Classical symptoms of typical pneumonia such as fever, rigors, chills, cough with rusty-colored sputum and dyspnea.

Signs
- Herpes labialis
- Mental confusion
- Signs of consolidation such as decreased chest movement, increased vocal fremitus, dull percussion note, bronchial breath sounds and crepitations.

Complications
Bacteremia, meningitis, endocarditis, pericarditis and empyema.

Investigations
- *X-ray chest*: By the second or third day of illness, x-ray chest shows lobar consolidation, but may be patchy.
- *Blood CP/ESR:* Leukocytosis 15,000-30,000 cells/μL with neutrophila but leukopenia may be observed with fulminant infection. ESR is > 100.
- *Sputum gram – stain:* may show gram-positive diplococci.
- *Blood culture*: positive in 20-25% of cases.
- *Pneumococcal antigen test.* Serologic test of sputum, urine and serum for pneumococcal antigen is 3-4 times more sensitive than sputum or blood cultures.

Treatment
Discussed in previous section of community – acquired pneumonia.

STAPHYLOCOCCUS AUREUS
- Staphylococcus aureus normally causes pneumonia only after a preceding influenzal viral infection. The infection starts in bronchi leading to patchy areas of consolidation in one or more lobes, which breakdown to form abscess.
- Presentation is similar to that of streptococcus pneumoniae, but characteristically it causes abscess formation in up to 25% of patients and empyema in 10%. Septicemia develops with metastatic abscesses in other organs such as brain, bones.
- X-ray chest shows patchy opacities, abscess may be present.
- Blood culture is usually positive
- Treatment: Cephalosporin or vanomycin

H. INFLUENZAE PNEUMONIA
- Mostly patients with this pneumonia has underlying COPD.
- Involvement of lower lobes more often than upper lobes.
- The amount of sputum production is significant
- Sputum gram stain shows small coccobaciallary gram negative organisms.
- Chest x-ray shows lobar pneumonia.
- Treatment:
  1. Cefaclor (Tab. Ceclor MR 750 mg) orally 12-hourly. OR
  2. Cefuroxime (Inj. Zinacef) 1g 8 hourly OR
  3. Third-generation cephalosporin such as ceftriaxone Inj. Rocephin) 1-2 g once daily.
  4. Levofloxacin or clarithromycin may be used.

MYCOPLASMA PNEUMONIA

This is common cause of atypical pneumonia. It often occurs in young previously healthy persons in their teens & twenties (i.e. young adults & children) frequently amongst those living in boarding houses (hostels).

Clinical features

Patient presents with atypical pneumonia in which extrapulmonary features are predominant and features of lower respiratory tract infection (signs and symptoms of pneumonia) are minimal while the x-ray is suggestive of pneumonia.

Pulmonary features:

Sore throat and hacking non-productive cough.

Extrapulmonary features

- Constitutional symptoms: fever, malaise, headache, arthralgias and chills.
- Skin: rash, erythema nodosum and erythema multifome.
- CNS: meningitis, encephalitis, transverse myelitis, cranial nerve or peripheral neuritis.
- Ear: bullous myringitis and otitis media.
- CVS: myocarditis, pericarditis and *hemolytic anemia.*
- GIT: nausea, vomiting and diarrhea.

Investigations

- Diagnosis is confirmed by a rising antibody titer > 1:32 or four fold rise
- Gram stains of sputum (if obtainable) reveal neutrophils but no dominant bacterial pathogen
- WBC count not raised.
- Chest x-ray: It shows patchy, nonlobar usually unilateral but may be bilateral infiltrates involving lower lobes often appearing as streaks radiating from hilus to the base.

Treatment

Two to three weeks course of one of the following antibiotics:

- Erythromycin 500mg every 6 hourly.
- Clarithromycin (Klaricid) 500mg 12-hourly.
- Tetracycline 500mg 6-hourly.
- Doxycycline 100mg 12-hourly.

LEGIONELLA PNEUMONIA

Lagionella pneumophilia transmitted through water droplets originating from infected water sources such as cooling system, air conditioning units and showers causes atypical pneumonia

Sporadic cases also occur where the source of infection is unknown. Risk factors are smoking, chronic lung disease, immunosuppression, old age, cancer and diabetes. Male is affected twice as commonly as females.

Symptoms

- Headache, high grade fever with rigors, myalgia, malaise.
- About 50% patients have gastrointestinal symptoms such as nausea, vomiting, diarrhea and abdominal pain.
- Mental confusion may be present.
- Haematuria occurs and occassionaly renal failure develops.
- Dyspnea with initially dry cough that later may become productive and purulent.

Signs

- Fever, relative bradycardia.
- Mental confusion.

Investigations

- Hyponatremia, hypophosphatemia, hypoalbuminemia.
- Liver enzymes: Aminotransferases are raised.
- X-ray chest: X-ray shows patchy or lobar consolidation with or without pleural effusion.

Diagnosis

- Legionella antibody titer of 1:128 is suspicious and a fur-fold increase in titer is diagnostic, however up to 8 weeks are required for seroconversion.
- Direct immunofluorescent staining of the organism in the pleural fluid, sputum or bronchial washings is the quickest way of diagnosis.
- A strong presumptive diagnosis of legionela infection is possible in majority of patients if they have three of the four following feature:
  1. A prodromal virus like illness.
  2. A dry cough, confusion or diarrhea
  3. Lymphopenia without marked leukocytosis
  4. Hyponatremia

Treatment

One of the following drugs may be given:

- Erythromycin 1g iv 6- hourly followed by 500 mg orally 6- hourly for 2-3 weeks.
- Levofloxacin (Cravit 500 mg) daily iv or orally.
- Clarithromycin 500 mg 12-hourly.
- Azithromycin 500mg then 250mg orally daily
- Ciprofloxacin (Ciproxin) 500 mg 12-hourly.
- Rifampicin may be added in ill patients.

GRAM NEGATIVE BACILLI PNEUMONIA

Gram negative bacilli are the cause of many hospitals acquired pneumonias but they are occasionally responsible for some cases in the community. Predisposing factors are debilitating diseases such as chronic alcoholism, neutropenia, cystic fibrosis, diabetes mellitus, malignancy and chronic diseases of heart, lung or kidney.

Klebsiella pneumoniae, pseudomonas and E. coli are common pathogens.

Klebsiella pneumonia

Pneumonia due to klebsiella usually occurs in elderly with history of lung disease, diabetes, alcohol abuse or malignancy.

Clinical features

- Sputum is purulent, gelatinous or blood stained and in large amount.
- Upper lobes are most commonly affected
- Sudden onset with severe systemic upset.

Investigations

- Blood and sputum culture.
- X-ray Chest: PA view shows opacities in upper lobes and lateral view shows bulging of the fissures occurring due to swelling of the infected lobes.

Management

- Inj. Gentamycin 80mg i.v 8 hourly.
- Inj. Ceftazidime (Fortum) 1-2gm i.v. 8-hoursly.

Pseudomonas pneumonia

- Pneumonia due to this organism may occur in patients with prolonged ventilation, COPD, CHF, diabetes, alcoholism and neutropenia.
- It causes microabscess, alveolar hemorrhages and necrotic areas.
- Sputum gram staining shows Gram-negative rods.
- X-ray Chest shows patchy infiltrates and cavitation.
- Investigations: blood & sputum culture.

Treatment:

- Ceftazidime (Inj. Fortum) 2g 8-hourly OR
- Ciprofloxacin (Inj. Ciproxin) 500mg 12-hourly plus tobramycin (Inj. Nebcin 80mg) 3-5 mg/kg/d in three or four divided doses i.v.

VIRAL PNEUMONIA

- Severe headache, malaise & anorexia are characteristic features in early stage.
- Spleen may be palpable in the 1st week.
- Fever & toxemia usually precede the respiratory symptoms by several days i.e. initially respiratory symptoms are not predominate, as they are dominant in bacterial pneumonia.
- X-ray chest: shows homogenous opacities with ill-defined edges
- White cell count is normal.
- Physical signs in the chest appear later and are seldom gross.
- Management: It is self-limiting disease. Fever usually subsides after 5-10 days. Only symptomatic management is required.

HOSPITAL-ACQUIRED (NOSOCOMIAL) PNEUMONIA

Pneumonia developing more than 48 hours after admission to the hospital is called hospital-acquired pneumonia. This time period of 48 hours is to exclude any infection present at the time of admission. Gram negative organisms are mainly responsible for nosocomial pneumonia.

Organisms

Gram negative bacilli (60%) e.g., E. coli, Pseudomonas, enterobacter, klebsiella, proteus

Streptococcus neumoniae (10%).

Staphylococcus aureus (10%).

Anaerobes.

Predisposing factors

Colonization of pharynx and stomach with bacteria is the most important step in the pathogenesis of nosocomial pneumonia. This colonization is predisposed by the following hospital and patient related factors:

Hospital factors

- Instrumentation of upper airway with nasogastric and endotracheal tubes.
- Contamination by dirty hands and equipments.
- Treatment with broad spectrum antibiotics that promotes the emergence of drug resistant organisms.
- Infected iv cannula.

Patient factors

- Malnutrition, advanced age, altered consciousness, reduced cough reflux, swallowing disorders and underlying pulmonary and systemic disease.
- Reduced immune defense (due to use of steroids, diabetes or malignancy)
- Aspiration of gastric secretions
- Bacteremia

Clinical features

Clinical features are similar to features of community- acquired pneumonia.

Investigations

- Blood culture from 2 different sites.
- Arterial blood gases.
- Pleural tap in case of pleural effusion.
- Chest x-ray may show patchy or lobar consolidation.
- Endotracheal aspiration using sterile suction catheter or bronchoscopy with bronchoalveolar lavage to get lower respiratory tract secretions for analysis.
- Blood CP, sputum examination and blood biochemistry are usually not helpful for the diagnosis of specific cause.

Treatment

Aminoglycosides (such as amikicin or gentamycin) OR levofloxacin (Cravit)

Plus

Ceftazidime (Fortum 1g) iv 8- hourly OR
Imipenem (Inj. Tienam 500mg) iv 6-8 hourly.

Plus
Vancomycin

Augmantin or clindamycin may be added if there is aspiration pneumonia.

ASPIRATION PNEUMONIA

Aspiration of small amounts of orophryngeal secretions occurs during sleep in normal individuals and rarely causes disease. Aspiration of large amounts of material > 50 ml with a pH < 2.4 (such as gastric secretions) produces classic aspiration pneumonia.

Predisposing factors.

- Seizures, coma
- Tracheal intubation, general anesthesia
- Nasogastric tube
- Neurologic disorders
- Diaphragmatic hernia with reflux
- Aspiration of infected oropharyngeal contents during operation of nose or throat under general anesthesia.

Organisms

Mixed aerobic-anaerobic organisms

- Anaerobes: Mostly in community – acquired cases.
- E. Coli, klebsiella, pseudomonas and staphylococcus mostly in hospitalized patients who develop aspiration.

Clinical features

- Fever, malaise and weight loss.
- Cough with expectoration of foul smelling purulent sputum suggests anaerobic infection.

Management

Clindamycin (Inj. Dalacin) 600 mg IV 8 hourly. After improvement 300mg orally every 6 hourly or Augmentin 625 mg 8-hourly.

OR

Inj. Augmentin 1.2 g 8 hourly plus metronidazole (Inj. Flagyl) 500mg 8-hourly.

Duration of antibiotics: continue until the x-ray chest show improvement that may take a month or more.

Chest tube drainage required if patient develops empyema.

PNEUMONIA IN IMMUNOCOMPROMISED PATIENT

Pulmonary infection is common in immunocompromised patient. The immunocompromised patient is defined as:

- Patient with neutrophil count<100/μL.
- Patient taking prednisolone in a dosage of over 5mg/d.
- Patient with diseases causing defects of cellular or humoral immunity such as AIDS.

Organisms

- Gram negative bacilli e.g. pseudomonas
- Opportunistic organism e.g. pneumocystis carnii (PCP), CMV, viral and fungal infections.

Treatment

Ceftazidime or ciprofloxacine plus vancomycin.

COMPLICATIONS OF NEUMONIA

Organism	Complication	X-ray
Streptococcus pneumoniae	Meningitis Endocarditis Pericarditis Septicemia Empyema	Lobar consolidation
H. influenza	Empyema Endocarditis	Lobar consolidation
Klebsiella	Cavitation Empyema	Lobar consolidation
Staph.aureus	Cavitation Empyema	Patchy infiltrates
Psuedomonas	Cavitation	Patchy infiltrates
E. Coli	Empyema	Patchy infiltrates
Anaerobes	Necrotizing pneumonia Abscess Empyema	Patchy infiltrates
Mycoplasma	Skin rash Bullous myringitis Hemolytic anemia	Extensive patchy infiltrates.
Legionella	Empyema Cavitation Endocarditis Pericarditis	Patchy or lobar

CASE PRESENTATION (LONG CASE) (PNEUMONIA)

Mostly of the lung cases of pneumonia are pneumococcal pneumonia therefore prepare pneumococcal pneumonia for long case and consider every question related to "Pneumonia" in contest of pneumococcal pneumonia until examiner specifies other particular types. Hospital acquired or nosocomial pneumonia is a favorite question of examiners.

History

- Distinguish between community acquired vs hospital acquired pneumonia.
- Consider age of the patient and pathogen
- Consider predisposing factors.
- Ask about symptoms e.g. fever, chills, cough, sputum, chest pain.
- Assess the severity of illness (see indications for hospitalization).

Physical Examination

- General physical examination including blood pressure, pulse temperature, respiratory rate and herpes labials.
- Examination of respiratory system e.g.
  (a) Inspection: Movement of chest.
  (b) Percussion: Percussion note (resonant, impaired, dull).
  (c) Auscultation: type of breathing (vesicular or bronchial). Crepitations.
- Examination of other systems to exclude complications of pneumonia.

Management

Initial or emire treatment in community acquired pneumonia (e.g. clarithromycin).
Specific treatment, if pathogen is identified
Side effects of drugs used for this illness.

Important viva questions

- Predisposing factors of different types of pneumonia.
- Indications for hospitalization.
- Complications of pneumonia
- Interpretations of investigations especially chest x-ray findings.
- Technique of percussion, findings of auscultation
- Empiric treatment of community –acquired pneumonia.

LUNG ABSCESS

Lung abscess is a localized collection of pus in a large cavity lined by chronic inflammatory tissue, from which pus has escaped by rupture into bronchus. It mainly results from anaerobic infection as a complication of aspiration pneumonia. X- ray chest shows a single thick – walled cavity with air- fluid level. Suppurative pneumonia caused by staphylococcus aureus, klebsiella and pseudomonas also cause lung parebchymal necrosis and abscess formation, however these are multiple abscesses.

ETIOLOGY

Aspiration pneumonia
Aspiration pneumonia results mainly from anaerobic organisms and usually involves the dependent lung zones such as posterior segments of upper lobes. Predisposing factors are discussed in previous section of aspiration pneumonia.

Poor dental hygiene and periodontal disease
They increase the number of anaerobic bacteria in aspirated material; dental procedure also increase the risk.

Suppurative pneumonia
Pneumonia caused by staphylococcus aureus, klebsiella or pseudomonas cause lung parenchyma necrosis and abscess formation. In suupurative pneumonia there are multiple cavities.

Spread from amebic liver abscess
Amebic abscess occasionally develop in right lower lobe following transdiaphragmatic spread from an amebic liver abscess.

CLINICAL FEATURES

Symptoms

- Onset may be acute or insidious i.e. patient may be toxic or non-toxic.
- High remittent fever with rigor and sweating
- Cough with large amount of sputum, which is sometimes fetid & blood-stained.
- Sudden expectoration of copious amount of sputum if abscess ruptures into a bronchus
- Pleural chest pain.

Signs

- Fever, weight loss and copious sputum
- Clubbing within 10-14 days.
- Signs of consolidation
- Pleural rub
- Poor dental hygiene

INVESTIGATIONS

X-ray Chest:

- A large dense homogenous lobar or segmental opacity surrounded by consolidation. An air-fluid level is usually present.
- In case of suppurative pneumonia there are multiple cavities within an area of consolidation.
- Empyema (presence of purulent fluid in pleural cavity) may also present.

D/D of cavity in the lung field:

- Tuberculosis
- Bronchogenic carcinoma
- Fungal infection
- Pulmonary infarction
- Wegner's granulomatosis
- Infected bullae and cysts

Ultrasound chest
Ultrasonography is useful for locating fluid and to reveal pleural loculations.

Sputum D/R shows pus cells, necrotic lung tissue.
Sputum culture and sensitivity.
Blood CP shows neutrophil leucocytosis

COMPLICATIONS

- Bronchiectasis
- Residual fibrosis

MANAGEMENT

- Clindamycin (Inj. Dalacin) 600 mg IV 8- hourly. After improvement clindamycin 300 mg orally every 6 hourly or Augmentin 625 mg 8 hourly. OR
- Inj. Augmentin 1.2 g 8-hourly plus metronidazole (Inj. Flagyl) 500mg 8-hourly.

Duration of antibiotics: continue until the x-ray chest show improvement that may take a month or more.

Chest tube drainage required if patient develops empyema.

Postural drainage: Percussion or clapping over the site of abscess with the patient in the postural drainage position is effective to expel secretions from the cavity.

EMPYEMA

The presence of pus in the pleural space is called empyema. It may involve the whole pleural space or only part of it (loculated or encysted empyema) and is almost invariably unilateral. The causative organism may or may not be isolated from the pus. For healing, empyema requires control of infection and proper drainage.

ETIOLOGY

Empyema usually arises after the rupture of a lung abscess into the pleural space or from bacterial spread from severe pneumonia or due to tuberculosis. About 40% patients with community- acquired pneumonia develop an associated pleural effusion (called parapneumonic effusion) and about 15% of these become secondarily infected.

CLINICAL FEATURES

An empyema should be suspected in patients with pulmonary infection if there is persistent or recurrence of pyrexia despite the continued administration of suitable antibiotics.

CLINICAL FEATURES OF EMPYEMA

Systemic features

- Pyrexia; usually high and remittent
- Rigors, sweating, malaise and weight loss
- Polymorphonuclear leukocytosis

Local features

- Pleural pain; breathlessness; cough and sputum usually because of underlying lung disease;
- Copious purulent sputum if empyema ruptures into a bronchus (bronchopleural fistula)
- Clinical signs of fluid in the pleural space.

INVESTIGATIONS

X-ray chest

Chest x-ray shows pleural effusion. A horizontal "fluid level" may be present when there is bronchopleural fistula producing pyopneumothorax.

Aspiration of pus

A wide bore needle is inserted through an intercostals space over the area of maximum dullness on percussion. This confirms the presence of empyema. Pus C/S may help to determine the cause of empyema.

MANAGEMENT

Tuberculous empyema

Anti-tuberculous therapy is started immediately and drainage with chest tube is required.

Parapneumonic effusion

Pleural effusion due to pneumonia is called parapneumonic effusion; it develops in about 40% patients of community –acquired pneumonia. Parapneumonic effusion usually responds to systemic antibiotics, however it must be decided whether to drain this fluid or not because it can organize and cause permanent loss of lung function.

Parapneumonic effusion may be 'uncomplicated' characterized by no pleural infection and normal pleural fluid pH and glucose. Such effusion is likely to resolve spontaneously and there is no need to drain.

In "complicated" parapneumonic effusion, pleural fluid is either frank pus or has potential to organize manifested by low pH, low glucose and high LDH.

Indications of drainage

Drainage with chest tube is required for parapneumonic effusion if any of the following is present:

- The fluid resembles frank pus or bacteria are seen on Gram stain.
- Pleural fluid glucose is <40 mg/dl.
- Pleural fluid pH is < 7.2
- Pleural fluid LDH> 1000 units/L.

Chest tube: An intercostals tube is inserted into the most dependent part of the empyema and connected to a water seal drain system.

A parapneumonic effusion that does not respond to drainage within 24 hours may have become loculated. Intrapleural injection of thrombolytic drug streptokinase via the chest tube (250,000 units in 100 ml 0.9% saline daily for up to 10 days may accelerate drainage. Open surgical drainage may be necessary if these measures are ineffective.

TUBERCULOSIS

Tuberculosis is a communicable, chronic, granulomatous disease, caused by mycobacterium tuberculosis. It usually involves the lungs but may affect any organ or tissue of the body.

ETIOLOGY

There are three types of mycobacteria which are responsible for disease in man.

1. Mycobacterium tuberculosis: the cause of most infections in human.
2. Mycobacterium bovis: endemic in cattle, but now rarely responsible for disease in human being except who use unpasteurized milk.
3. Atypical or opportunistic mycobacteria affecting immunocompromised persons such as with AIDS.

SPREAD OF INFECTION

- *Direct droplet spread:* it mean from person to person by inhalation of air-borne bacilli that have been coughed or sneezed into the atmosphere.
- *Indirect spread;* via dishes, clothing and other article of daily use laden with bacilli.
- *Via ingested milk:* Ingestion of contaminated milk causes infection of Bovis type of bacilli.

PREDISPOSING FACTORS

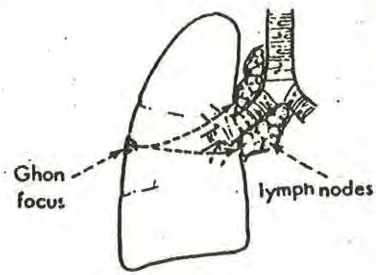
1. *Environmental factors*: which lower the body resistance such as: malnutrition, poverty, overcrowding unhygienic conditions, alcoholism & heavy smoking.
2. *Pathological factors*: which lower the body resistance e.g. diabetes mellitus, steroids, chronic lung disease, lymphoma and cytotoxic drugs.

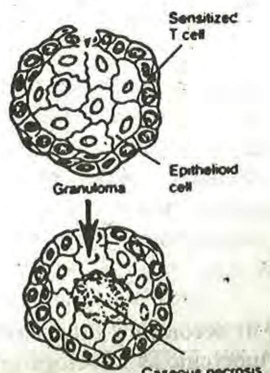
TYPE OF TUBERCULOSIS

1. Primary tuberculosis.
2. Post-primary (secondary tuberculosis)

PRIMARY TUBERCULOSIS

It is a form of disease that develops in a previously unexposed and therefore nonsensitized individual, usually in children. Primary tuberculous infection usually occurs in the lung but occasionally in the tonsils or ileocecal region. The primary focus of infection is called Ghon focus which mostly occurs subpleural at the lower part of upper lobe or upper part of lower lobe. Then the tubercle bacilli reach the draining lymph nodes at the hilum of the lung within an hour. Initially there is neutrophil infiltration that is replaced by macrophages that ingest bacilli and stimulate T –cell mediated immunity that can be demonstrated 3-8 weeks after the initial infection by a positive tuberculin reaction.





Clinical features

- Asymptomatic in majority of patients, diagnosis only on x-ray chest and tuberculin test.
- Mild fever: lasts for 7-14 days.
- Dry cough – mild.
- *Erythema nodosum:* Bluish-red raised tender cutaneous lesions on the shins and less commonly on the thighs may occur in primary tuberculosis. It may also occur in other conditions e.g. sarcoidosis, streptococcal infection.

FATE OF PRIMARY TUBERCULOSIS

- Healing and calcification
- Progressive pulmonary tuberculosis
- Post-primary tuberculosis

Healing

In most people, the primary infection and the associated lymph node lesions heal and calcify.

Progressive pulmonary tuberculosis

- In children with impaired immunity, such as those with malnutrition the primary infection does not heal and leads to primary progressive pulmonary disease characterized by enlargement, caseation and cavitation of primary focus and spread of infection to other sites of lung and pleura causing pleural effusion.
- Enlarged lymph nodes may compress bronchi, causing obstruction and subsequent segmental or lobar collapse.
- Progressive pulmonary tuberculosis may appear either during the course of the initial illness or after a latent interval of weeks or months.
- Hematogenous spread of infection is common causing granulomatous lesions involving mostly lungs, bones, joints and kidney. Usually healing takes place, however immunocompromised patient may develop miliary tuberculosis and/or tuberculous meningitis.

Post-primary or secondary tuberculosis

This type of tuberculosis develops in previously sensitized host resulting from re-infection or most commonly reactivation of primary dormant infection. It may occur shortly after primary tuberculosis, but mostly it develops decades after the initial infection, particularly when host's resistance is weekend. Characteristics of this tuberculosis are involvement of upper lobe, and superior segments of lower lobes and cavitatory lesions. Post –primary or secondary tuberculosis will be discussed later in detail because this is the main form of disease with which patient present in medical units and physicians.

MANAGEMENT

Anti-Tuberculous Therapy (ATT).

INVESTIGATIONS IN PRIMARY TUBERCULOSIS

X-ray chest:

- Children – unilateral hilar lymph node enlargement, the accompanying intrapulmonary lesion may or may not be seen.
- Adolescents and young adults – lymph node enlargement less conspicuous but pulmonary lesion more prominent.

Tuberculin test

Extremely valuable in children. A positive test in a child who has not previously been vaccinated with BCG must be assumed to indicate active disease.

Bacteriological examination

Sputum seldom available. If not, 3 laryngeal swabs or fasting gastric washings should be examined. Isolation of tubercle bacilli provides absolute proof of diagnosis.

MILIARY TUBERCULOSIS

Miliary tuberculosis is the result of acute diffuse dissemination of tubercle bacilli via the blood stream. It mostly occurs in the children and young adults as a complication of primary tuberculosis however it may also occur in old patients.

Onset

Usually rapid onset in children and young adults while gradual onset in adults and elderly.

Clinical features

<u>In children</u> there is high-grade fever with drenching sweats during sleep, marked tachycardia, loss of weight and progressive

anemia. Cough and shortness of breath are occasionally present.

- Choroidal tubercle may be visible in eye on opthalmoscopy.
- Liver is often enlarged and spleen may be palpable.
- Leukocytosis is usually absent.
- Occasionally the disease presents as tuberculous meningitis.

In adults there is vague, ill health, low-grade fever and weight loss. Chest symptoms and choroidal tubercle are rare. Liver and occasionally spleen may be enlarged.

Investigations

1. *X-ray chest:*

X-ray chest shows characteristic "miliary mottling" symmetrically distributed throughout both lung fields. X-ray may be normal, as the tubercles are not visible until 1-2 mm in diameter and until seen throughout the lung. Sarcoidosis and staphylococcal or mycoplasma pneumonia can mimic the x-ray appearance of miliary tuberculosis.

2. *Mantoux Test (MT)*

Mantoux test is *usually positive*, however negative test does not rule out acute miliary tuberculosis because tuberculin sensitivity is occasionally depressed in people with very severe disease.

3. *Biopsy and culture of liver and bone marrow*

They may be necessary in patients presenting with pyrexia of unknown origin (PUO).

4. *Trial of anti-tuberculous therapy*

A trial of anti- tuberculous therapy may be used in individuals with PUO. The fever should settle within two weeks of starting ATT if it is due to tuberculosis. This approach is used in susceptible individuals when a diagnosis cannot be confirmed.

POST-PRIMARY TUBERCULOSIS (SECONDARY TUBERCULOSIS)

The term used to describe lung disease the characteristic pathological features of which is the tuberculous cavity, formed when the caseated and liquefied center of tuberculous pulmonary lesion (granuloma) is discharged into the bronchus. Massive involvement of pulmonary segments or lobes, with coalescence of lesions produces *tuberculous pneumonia.*

Post-primary tuberculosis develops in previously sensitized host resulting from reinfection or reactivation of dormant primary infection.

Common sites

It is almost always localized to apices of one or both upper lobes. In addition, the superior segments of lower lobes are frequently involved. In these locations there is high oxygen concentration that favors myocobacterial growth.

CLINICAL FEATURES

Systemic symptoms

Lowe- grade intermittment fever usually in the evening, night sweats, weight loss, anorexia, malaise and weakness.

Local symptoms (related to pulmonary system)

- *Cough*: An early symptoms, initially often dry and hacking, later productive with sputum.
- *Sputum:* Usually mucoid at first but later becomes purulent.
- *Hemoptysis:* It may be mild as blood streaks in sputum or massive as a result of erosion of vessel in the wall of cavity.
- *Chest pain:* Dull ache in the chest due to pleurisy.
- *Dyspnoea:* Late symptom, may be due to fibrosis, pleural effusion or spontaneous pneumothorax.

On examination

- Physical signs depend on stage and extent of disease. In initial stages signs are usually none, diagnosis being radiological.
- Patients may have crepitations in the involved area during inspiration. Fever and wasting may be present. In some patients pallor due to anemia and finger clubbing develop.

Following signs may be present:

Signs of consolidation

- Decreased movement over affected part of the chest.
- Impaired percussion note
- Bronchial breath sounds.

Signs of cavitation

- Impaired or tympanic note if the cavity is large
- Bronchial breath sounds.
- Crepitations.

Signs of fibrosis

- Affected side of the chest flattened.
- Apex beat displaced to the side of lesion
- Chest expansion is required
- Percussion note impaired

Signs of pleural effusion

- Movement of the chest reduced
- Mediastinum is shifted towards opposite side
- Percussion note is stony dull
- Breath sounds diminished or absent.

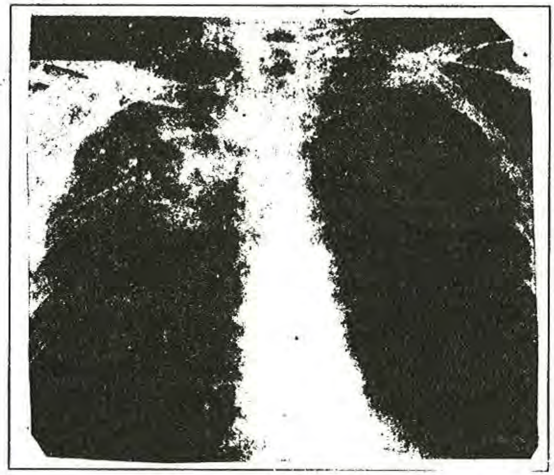
Clinical presentations of pulmonary TB

- Chronic cough with hemoptysis
- Weight loss
- Pyrexia of unknown origin
- Unresolved pneumonia
- Exudative pleural effusion
- Asymptomatic
- Pneumothorax

INVESTIGATIONS

1. X-ray chest: (P.A. view)

- At an early stage ill-defined opacity or opacities (nodular or reticulonodular opacitieis), usually situated in one of the upper lobes.
- In advanced cases, opacities are larger and more widespread and may be bilateral.
- An area or areas of translucency within the opacities indicate cavitation.
- Trachea and heart shadow are displaced towards the side of lesion in marked fibrosis
- If pleural effusion is present, a dense uniform opacity in the lower and lateral part of the hemithorax, forming crescenteric upper border.
- If pneumothorax is present, the x-ray shows the sharply defined edge of the collapsed lung. Between this edge and chest wall there is complete translucency with no lung marking.



CAUSES OF LUNG CAVITATION

- Tuberculosis
- Bronchiectasis
- Bronchogenic carcinoma
- Lung abscess
- Pneumonia caused by staphylococcus, pseudomonas or legionella.

2. Sputum for AFB smear

Microscopic examination of at least three specimens of sputum, preferably collected early in the morning is performed for acid –fast bacilli. Sputum induction by nebulization of hypertonic saline or other methods are helpful in patients who are not producing sputum.

3. Tuberculin test

The tuberculin skin test is positive in individuals who have been infected sometime with mycobacterium tuberculosis, but does not distinguish between current disease and past infection.

Mantoux test (MT)

In the Mantoux test 0.1 ml of standard purified protein derivative (PPD) is injected on the anterior surface of forearm using a 27-gauge needle. The

transverse width (in mm) of the induration at the skin test site should be recorded after 48-72 hours.

A negative mantoux test does not rule out the diagnosis of tuberculosis while the positive test may be helpful in the diagnosis. Test is positive if the induration is 10 mm or more in diameter.

MT should be considered positive if > 5mm for patient with HIV and close contacts of patient with active tuberculosis.

False positive MT: tuberculin test may be falsely positive without disease due to infection with nontuberculous mycobacteria.

False negative MT: tuberculin test may be negative in the presence of infection with mycobacterium tuberculosis because of weak immunity as a result of malnutrition, old age, immunodeficiency states such as AIDS, corticosteroid therapy, chronic renal failure, fulminant tuberculosis. It may be negative due to improper testing technique.

ESR

ESR should no be relied upon in the diagnosis of tuberculosis. It may be high or remain normal.

Heaf test and Tine test

In Heaf test and Tine test small amount of PPD is injected on flexor surface of left forearm via 6-pointed disposable apparatus. This is a simple test used for screening and commonly performed in wards.

4. Pleural fluid aspiration

In tuberculosis pleural fluid is exudates with predominant lymphocytes. Pleural fluid culture for mycobacterium tuberculosis is positive in less than 25% of cases but the diagnostic yield is increased if pleural biopsy is performed along with pleural aspiration.

5. Polymerase Chain Reaction (PCR)

PCR permits rapid detection of mycobacterial DNA in sputum and other fluids within 48 hours and is becoming common test for detection of mycobacterium tuberculosis.

6. Needle biopsies

Biopsy of pleura, lymph nodes and solid lesion within the lung (tuberculomas) may reveal granuloma; biopsies may be cultured.

7. Culture

Mycobacteria are slow growing and therefore culture for tubercle bacilli takes about 4-8 weeks on solid medium such as Lowenstein – Jensen and a shorter time (2-3 weeks) on liquid medium such as BACTEC medium. This liquid medium is now preferred. Usually sputum culture is performed, if tissue is obtained (such as lymph node biopsy) it is critical that biopsy specimen should not be put in formaldehyde (Formaline), it is preserved in normal saline.

8. Drug sensitivity test

Sensitivity of first-line antituberculous drugs is performed with culture (indirect) or separately (direct). Direct sensitivity test is rapid and reports are available within 3 weeks. This sensitivity test is performed when treatment is failing and when sputum cultures remain positive after three months of therapy.

9. Fibreoptic bronchoscopy

Fibreoptic bronchoscopy with bronchial washing from the affected lobe is useful if patient is not producing sputum. Transbronchial biopsies may be obtained.

10. Gastric washing

If patient is not producing sputum and bronchoscopy is not available then gastric washing is obtained for culture. Early morning aspiration of gastric contents after an overnight fast is the gastric washing. This test is usually limited to pediatric patient to diagnose primary tuberculosis.

COMPLICATIONS OF PULMONARY TB

Pleurisy
With or without pleural effusion

Pneumothorax
May follow rupture of cavity into pleural space

Empyema or pyopneumothorax
Serious complications of rupture of a tuberculous lesion into the pleural space.

Tuberculous laryngitis
Usually only occurs in advanced pulmonary disease

Tuberculous enteritis
Follows swallowing heavily infected sutum in some patients with extensive pulmonary disease.

Ischiorectal abscess
Consider TB in all cases. Tubercle bacilli can pass through rectal mucosa

Blood-borne dissemination
Uncommon complication of post-primary pulmonary disease except in the immunosupressed

Respiratory failure and right ventricular failure
Late complications when disease has caused extensive pulmonary destruction and fibrosis

Fungal colonization of cavities
Cavities which persist after anti-tuberculosis treatment may become colonized with Aspergillus fumigatus and a ball of fungus may develop.

Review of investigations for diagnosis of tuberculosis

- Chest x-ray
- Sputum microscopy (AFB smear)
- Mantoux (Tuberculin) test
- Pleural fluid D/R, AFB culture
- Pleural biopsy
- Bronchial washing and biopsy for AFB smear and culture.
- PCR for M. tuberculosis
- Biopsies of lymph node, liver, bone marrow

TREATMENT

Treatment for tuberculosis should be started as soon as AFB smear is positive in 2 laboratory reports. A competent physician should decide treatment for tuberculosis with a single positive report or smear negative (AFB negative) cases based on clinical examination and chest X-rays.

There are two phases of antituberculous therapy:

Initial phase: This is the bactericidal phase in which majority of tubercle bacilli is killed, symptoms resolve and the patient becomes non-infectious. Duration is 2 months.

Continuation phase: This is the phase of sterilization in which remaining tubercle bacilli are eliminated and the organ is sterilized. Duration of this phase is 7 months.

DURATION 8 MONTHS

Initial phase 2 months 4 drugs

1. Isoniazid (INH) along with pyridoxine (vit. B6).
2. Rifampicin
3. Ethambutol or streptomycin
4. Pyrazinamide

Continuation phase 6 months 3 drugs

1. Isoniazid along with pyridoxine (Vit. B6)
2. Rifampicin
3. Ethambutol

Note: due to high resistance we continue 3 drugs in continuation phase including ethambutol in Pakistan.

Combination therapy

Antituberculous drugs are given in combination to prevent resistance because mycobacteria develop resistance easily against single drug. These drugs are given ½ hour before breakfast because absorption of antituberculous drugs especially absorption of rifampicin is impaired with food. Few patients do not tolerate antituberculous therapy in empty stomach and develop vomiting; in such patients rifampicin is given before and remaining drugs after breakfast.

Directly observed therapy short course (DOTS)

One of the major causes of treatment failure is the noncompliance of the patient because of longer treatment, poverty as the patient is unable to purchase drugs and a large number of tablets. To treat this communicable disease and to overcome this problem of noncompliance a health care worker physically observes the patient ingest antituberculous medication in the home, clinic or hospital 3 times per week. Free drugs and breakfast may be another incentives. To reduce the number of tablets combination preparations may be used in which antituberculous drugs are combined in one tablet. Dosage of drug is increased about 50% (*Example*: if a patient is getting drug 5 mg/kg/daily, in DOTS he is given 7.25 mg/kg/ three times per week).

Duration of treatment

Duration of pulmonary tuberculosis is 9 months while the extra-pulmonary tuberculosis such as tuberculous meningitis and tuberculosis of bone and joints and miliary tuberculosis require longer treatment of about one year.

Monitoring of the response to treatment

- Clinical assessment, improvement in symptoms.
- Sputum AFB smear monthly until it becomes negative. By the end of third month of treatment all patients should be smear negative. When the patient's sputum remains positive at or beyond 3 months, treatment failure or drug resistance should be suspected.
- Chest x-ray is performed initially and at the end of treatment for comparison. Serial chest x-ray is not recommended because improvement in x-ray lags behind the clinical and bacteriologic response.

- A base – line LFTs should be done because hepatitis is the major side effects of ATT and baseline LFTs are required for comparison. In about 20% patients there is rise in AST (up to three times of upper limit) but the drugs are continued until AST is markedly raised or patient develops symptoms of hepatitis. When
- When the liver functions return to normal ATT is again started one at a time and determine which drug caused hepatitis, this drug is replaced by another drug.

DOSAGE OF FIRST-LINE ANTI-TUBERCULOUS DRUGS

Drug	Dose mg/kg	<33 kg	33-50 kg	>51 kg
Isoniazid	5	200	300	300
Rifampicin	10	300	450	600
Ethambutol	15-25	800	1200	1600
Pyrazinamide	15-30	1000	1500	2000
Streptomycin	15	500	750	1g

DOSAGE OF FIRST-LINE ANTI-TUBERCULOUS DRUGS

Drug	Dose mg/kg	Dose mg/kg in DOTS if given 3 times /week
Isoniazid	5 max. 300mg	15 max. 900mg
Rifampicin	10 max. 600mg	10 max. 600mg
Ethambutol	15-25 max. 2.5g	25-30 max. 2.5g
Pyrazinamide	15-30 max.2g	50-70 max.3g
Streptomycin	15 max. 1g	25-30 max.1.5g

SINGLE PREPARATIONS

Generic name	Proprietary	Strength
Isoniazid (NH)	Isoniazid	Tab. 100mg
Rifampicin	Lederrif	Tab. 300mg Tab. 450mg Tab. 600mg
Ethambutol	Myambutol	Tab. 400mg
Pyrazinamide	PZA-CIBA	Tab. 500mg
Stretomycin	Polybiotic	Inj. 0.5 & 1g

COMBINATIONS

Drug	Contents in mg
Myambutol INH	Tab. Ethambutol 300 mg + INH 100mg
Rifinah	Tab. 150mg: INH 100 + Rif 150 Tab. 300mg: INH 150 + Rif 300 Tab. 450mg: INH 300 + Rif 450
Rimactazied	Tab. 300mg: INH 150 + Rif 300 Tab. 450mg: INH 300 + Rif 450
Rifater	Tab: INH 50 + Rif 120+ PZA 250
Myrin P	Tab: INH 60 + Rif 120 + Ethambutol 225 + PZA 300
Myrin	Tab: INH 75 + Rif 150 + Ethambutol 300 One tablet / 15 kg weight once a day

Sample prescription Weight = 50

- Tab. INH 100 mg 3 OD
- Tab. Rifampicin 450 mg 1 OD
- Tab. Ethambutol 400 mg 3 OD
- Tab. Pyrazinamide 500 mg 3 OD
- Tab. Pyridoxine (vit B6) 50 mg 1 OD

ROLE OF CORTICOSTEROID DRUGS TUBERCULOSIS

These agents suppress the cell-mediated reaction induced by the tubercle bacillus. But in this way they may promote a rapid dissemination of infection by interfering with tissue defense mechanisms. If however, a corticosteroid drug is given in conjunction with effective antituberculous chemotherapy, it may reduce severity of the local inflammatory reaction and of the associated systemic disturbance without dissemination of the infection.

In acute pulmonary tuberculosis such treatment will rapidly relieve fever and dramatic improvement in radiological appearance.

Corticosteroids may save the lives of patients with severe infection by enabling them to survive until antituberculous chemotherapy has had time tc expert its influence.

Indications

- Tuberculous meningitis
- Genitourinary tuberculosis
- Miliary tuberculosis
- Acutely ill patient
- Widespread infiltration
- TB in serous sacs such as peritonitis, pleural or pericardial effusion.
- Large lymph nodes compressing trachea or bronchi.

Second- line drugs for tuberculosis
• Ofloxacin
• Ethionamide
• Cycloserine
• Para-aminosalicylic acid (PAS)
• Amikicin
• Kanamycin
• Capreomycin

TREATMENT FAILURE

Treatment failure is said when the patient's sputum culture remains positive after 3 months or AFB smear remains positive after 5 months.

Send specimen for culture and sensitivity and do not change treatment until you get C/S report however if the condition of the patient is deteriorating then add at least two or three drugs that have never been used before.

DRUG RESISTANT TUBERCULOSIS

Drug resistance usually develops when patient uses single drug therapy or irregular in taking properly prescribed therapy.

Primary drug resistance tuberculosis

In this type a strain infecting a patient who has not previously been treated.

Acquired drug resistance tuberculosis

Acquired resistance develops during the course of treatment with an inappropriate regimen.

Multi-Drug Resistant (MDR) tuberculosis

When the organism is resistant to more than one drug, it is called multidrug resistance tuberculosis. In these patients combination of three drugs chosen from second line anti-ruberculous therapy such as ethionamide, cycloserine, para-aminosalicylic acid (PAS), and ofloxacin plus one drug chosen from amikacin, kanamycin, and capreopycin. Duration of treatment is 24 months. (Second – line drugs are less effective, more toxic and more expensive than the first – line drugs).

SOME IMPORTANT TERMS

New case
A patient who has never had treatment for tuberculosis or has taken anti-tuberculous drugs for less than 4 weeks.

Relapse
A patient declared cured in the past who again has a positive AFB sputum smear.

Failure cases
Patients who remain, or become, sputum smear-positive 5 months or more after commencing treatment.

Chronic cases
A patient who remains AFB smear positive even after completing a re- treatment regimen under supervision.

Treatment after default
A patient who returns to treatment after having interrupted treatment for two months or more.

WHO CATEGORIES OF TUBERCULOSIS	
Category I	• New sputum + ve pulmonary TB • New sputum -ve pul. TB with extensive parenchymal involvement. • New cases of severe form of extrapulmonary TB
Category II	• Relapse • Treatment failure • Interrupted or default treatment
Category III	Sputum –ve pul. TB with limited parenchymal involvement
Category IV	• Extrapulmonary TB (less severe form) • Chronic cases

CLINICAL GUIDLINE FOR THE MANAGEMENT OF TUBERCULOSIS

Tuberculous patients are divided into 4 categories for the management: .

CATEGORY 1: NEW CASE

A patient who has never had treatment for tuberculosis or has taken anti- tuberculous drugs for less than 1 month. This group includes the following:

- Smear positive pulmonary tuberculosis
- Smear negative pulmonary tuberculosis
- Extrapulmonary tuberculosis

Treatment (duration 8 months)

Initial intensive phase (2 months) 4 drugs

Isoniazid, rifampicin, ethambutol and pyrazinamide

Continuation phase (6 months) 2 drugs

Isoniazid and ethambutol (or rifampicin) for 6 months

Check sputum smear after 2 months

- If smear negative continue isoniazid and ethambutol for 6 months.
- If smear positive then continue 4 drugs for additional 1 month and 2 drugs for next 5 months.

Sputum smear should be checked at the end of 2nd, 5th, and 8th month in sputum smear positive patients.
If sputum smear is positive at the end of 5 months of treatment, there is likelihood of drug resistance. These patients are labeled as treatment failure and should be referred to a chest specialist.

CATEGORY 2: RE- TREATMENT CASES

In this category those patients are included who have taken anti- tuberculous therapy in the past such as following:

- *Relapses:* a sputum smear positive patient who was declared cured in the past, after completing a course of anti- tuberculous therapy.
- *Treatment failure*: patients who remain, or become sputum smear positive 5 months or more after beginning of treatment.
- *Smear positive patients who have taken ATT for more than one month and defaulted (stopped medicines)*

Treatment ((duration 8 months)

Initial intensive phase (2 months) 5 drugs

Isoniazid, rifampicin, ethambuto, pyrazinamide and streptomycin.

One month more

Isoniazid, rifampicin, ethambuto, pyrazinamide but no streptomycin.

Check sputum smear after 3 months

- If smear negative: continue isoniazid, rifampicin and ethambutol for 5 months.
- If sputum is still positive: Give 5 drugs again for one month

Check sputum smear again after 4 months

If smear is still positive send sputum for culture and sensitivity and continue isoniazid, rifampicin and ethambutol for 4 months whether the smear is positive or negative.

Check sputum after 8 months

If sputum is positive at the end of treatment i.e. after 8 months then this is called chronic case and refer the patient to chest specialist.

CHARACTERISTICS OF ANTI-TUBERCULOUS DRUGS			
Drug	**Most common Side-effects**	**Tests for Side-effects**	**Remarks**
Isoniazid	• Peripheral neuritis • Hepatitis • Hypersensitivity	• Sensory system examination • ALT and AST	• Bactericidal • Acting in both extracellular and intracellular organisms • Add pyridoxine for prophylaxis
Rifampicin	• Hepatitis • Fever • Thrombocytopenia	ALT, AST, platelets	• Bactericidal to all populations of organisms. • Orange or pink color of urine and other body secretions • Oral contraceptive may not be effective, other methods should be used.
Ethambutol	• Reversible optic neuritis. Patient is unable to differentiate red from green, there may be scotomas. • Hypersensitivity rash	• Red-green color discrimination • Visual acuity	• Bacteriostatic to all intracellular and extracellular organisms. • Should not be used in children under 3 years and elderly as it is difficult to test for optic neuritis • Use with caution in renal failure.
Pyrazinamide	• Hepatitis • Gout	• AST, ALT • Uric acid	• Bactericidal to intracellular organisms • Particularly useful in tuberculosis meningitis
Streptomycin	• 8th nerve damage • Nephrotoxicity	• Audiogram • BUN. Creatinine	• Bactericidal to extracellular organisms. • Use with caution in old and renal patient.

EXTRA-PULMONARY TUBERCULOSIS

Pleural tuberculosis

Involvement of pleura is common in tuberculosis resulting in chest pain due to pleurisy and pleural effusion causing shortness of breath. On examination patient has signs of pleural effusion, x-ray chest shows pleural effusion. Pleural biopsy reveals granulomas and culture is positive in 70% of cases. Pleural fluid D/R shows exudates characterized by:

- Protein concentration more than 50% of that of serum.
- A pH usually < 7.2
- WBC 500-2500 mainly lymphocytes. Neutrophils may predominate in the early stage. Pleural effusion in tuberculosis resolves spontaneously with ATT, however should be drained if patient is dyspnic.

Tuberculous empyma may occur that results from rupture of cavity, with delivery of large number of organisms into the pleural space. Chest x-ray shows pyopneumothorax with air fluid level. Effusion is purulent and thick and contains large number of lymphocytes. Surgical drainage with chest tube is required along with ATT. Tuberculous empyma may lead to pleural fibrosis and restrictive lung disease.

Tuberculosis of upper airways

Tuberculosis of larynx, pharynx and epiglottis is nearly always a complication of advanced cavitatory pulmonary tuberculosis. It manifests as hoarseness, dysphagia and productive cough. Ulceration may be visible on laryngoscopy, biopsy is required to confirm the diagnosis.

Lymph node tuberculosis

It is one of the most common extra-pulmonary tuberculosis. It presents as painless enlargement of lymph nodes, most commonly at cervical and supraclavicular sites. Lymph nodes are discrete in early stages and then become matted. Cold abscess may develop due to caseation and liquefaction of the nodes producing fluctuant swelling. Sinus formation is common. Diagnosis is established by fine – needle aspiration or surgical biopsy.

Tuberculous pericarditis

It may present subacutely or acutely with fever, chest pain and pericardial rub. Then pericardial effusion develops with features of cardiac temponade. Effusion is exudates and may be hemorrhagic. Constrictive pericarditis with thick pericardium, fibrosis and sometimes calcification is the main complication which may be prevented by glucocorticoid therapy along with ATT.

Gastrointestinal tuberculosis

Swallowing of the infected sputum, hematological spread and rarely ingestion of milk of cows infected with bovine strain are important pathological mechanisms involved in tuberculosis of gastrointestinal tract.

Intestinal tuberculosis

- Terminal ileum and cecum are most commonly involved.
- Abdominal pain, chronic diarrhea, malabsorption, intestinal obstruction, and palpable mass can result from tuberculosis of intestine. Barium studies may indicate ulceration and intestinal obstruction. Biopsy obtained by laproscopy or lapratomy is often needed for diagnosis.

Peritoneal tuberculosis

- Tuberculous peritonitis results either from direct spread of tubercle bacilli from ruptured lymph nodes or by hematogenous spread.
- Fever, pain and ascites may develop. Ascitic fluid is exudates with leukocytosis (predominantly lymphocytes).
- Peritoneal biopsy is often needed to establish the diagnosis.

Genito-urinary tuberculosis

- Hematuria, dysuria, increased frequency of micturition and flank pain may be the symptoms. However patient may be asymptomatic and presents first time with complications.
- "Sterile Pyuria" (pus cells but no bacteria in urine) in acidic urine should always be suspected due to tuberculosis. AFB cultures of three morning urine yield diagnosis in more than 90% of cases.

- Tuberculosis of fallopian tubes and endometrium can give rise to infertility, pelvic pain and menstrual abnormalities. In males tuberculosis involves epididymis, prostate or testis.

Bones and Joints tuberculosis
Tuberculosis of bones and joints mainly involves weight-bearing joints such as spine, hips and knee in that order. Tuberculosis of hip joint causes pain and limping while the tuberculosis of knee presents with pain and swelling of joint. Tuberculosis of spine presents as backache and then paraplegia.

Tuberculosis of spine Pott's disease)

- Tuberculosis of spine (Pott's disease) often involves two or more adjacent vertebral bodies. Lower thoracic and upper lumber vertebrae are more commonly involved in adults while upper thoracic vertebrae in children. Intervertebral disc is also destroyed.
- With advanced disease, collapse of vertebral bodies results in kyphosis (gibbus formation).
- A paravertebral cold abscess may also form.
- Main complication of Pott's disease is paraplegia due to spinal cord compression.
- MRI of spine is the investigation of choice while bone biopsy confirms the diagnosis.

Tuberculous meningitis and tuberculoma
Tuberculosis of CNS results from hematogenous spread of tubercle bacilli or rupture of subependymal tubercle into the subarachnoid space. In more than 50% cases x-ray chest gives evidence of old pulmonary lesion or miliary tuberculosis.

Presentation may be subacute with headache and mental changes or acute with confusion, lethargy, altered consciousness, and neck rigidity. Typically the disease evolves over 1 or 2 weeks--- a course longer than bacterial meningitis.

Cranial nerve palsy especially of ocular nerve is a frequent finding. Hydrocephalus is the main complication. Lumber puncture is diagnostic, CSF shows high protein, low glucose and high leukocyte count with lymphocytes predominant. CSF AFB is positive only in < 20% of cases while culture is positive in 80% of patients. MRI may show *basal enhancement* and hydrocephalus. Glucocorticoid therapy with ATT can prevent hydrocephalus formation.

Tuberculoma is a space occupying granulomatous lesion of brain due to tuberculosis and presents as seizures or weakness of any part of the body such as monoplegia, paraplegia. Contrast CT or MRI shows ring-lesions.

Adrenal glands tuberculosis
It can give rise to Addison's disease

SPECIAL CLINICAL SITUATIONS

Pregnancy: Streptomycin is contraindicated as it causes 8th nerve damage of fetus resulting in congenital deafness. Pyrazinamide is usually avoided since the risk of teratogenicity with pyrazinamide has not been clearly defined. Small concentration of antituberculous drugs are present in breast milk and is not harmful to nursing newborn, there fore breast feeding is not a contraindication while receiving antituberculous therapy by lactating mother.

Renal failure: Avoid aminoglycosides, ethambutol may be given if serum level can be monitored. For mild to moderate renal failure INH, rifampicin and pyrazinamide may be given in usual dose, in severe renal failure dose should be reduced except those undergoing hemodialysis.

Liver disease: in mild to moderate liver disease ATT may be given and monitoring is required. If patient clinically develops hepatitis or aminotransferases become very high then stop treatment. Hepatitis due to ATT usually subsides within a week, then start non-hepatotoxic or least hepatotoxic drug in small amount, if no hepatotoxicity give full dose within 2-3 days. In this way all drugs are checked and culprit drug is identified and stopped, while other drugs are given.
In severe liver disease tuberculosis should be treated with "SHE therapy" including S for Streptomycin, H for INH and E for Ethambutol. Rifampicin may be added. Close monitoring is required if rifampicin and INH are given while the Pyrazinamide should be avoided.

FUNGAL INFECTIONS OF RESPIRATORY SYSTEM

ASPERGILLOSIS

Aspergillus fumigatus is the usual cause of aspergillosis, though other species of aspergillus may cause a wide spectrum of disease. There are different presentations of aspergillosis such as:

- Allergic bronchopulmonary aspergillosis
- Intracavitary aspergilloma
- Extrinsic allergic alyeolitis
- Invasivepulmonary aspergillosis

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

This is caused by hypersensitivity reaction to aspergillus fumigatus involving the bronchial walls and peripheral parts of lung. In vast majority of patients it is associated with bronchial asthma but it can occur in non-asthmatic patients. It may cause bronchiectasis and lung fibrosis.

Clinical features

It presents with episodes of eosinophilic pneumonia throughout the year with fever, cough productive of bronchial cast that contains fungus, breathlessness and worsening of asthma.

Investigations

- Chest x-ray shows recurrent transient diffuse pulmonary infiltrates and lobar or segmental collapse.
- Peripheral blood eosinophilia.
- Very high serum 1gE antibodies.
- Positive skin test to an extract of aspergillus fumigatus.
- Antibodies against aspergillus fumigatus are detectable.
- Fungal hyphae of aspergillus fumigatus on microscopic examination of sputum.
- Pulmonary function test shows decrease on lung volume.

Treatment

Prednisolone (Deltacortil) 30mg/d readily clears pulmonary infiltrate. Frequent episodes can be prevented with long-term treatment with prednisolone 10-15mg/d.

INTRACAVITARY ASPERGILLOMA

Inhaled air-borne spores of aspergillus fumigatus may lodge and germinate in damaged pulmonary tissue and an aspergilloma **(fungal ball)** can form in any area of damaged lung in which there is persistent abnormal space such as tuberculous cavity (most common), lung abscess, bronchiectatic cavity or even cavitated tumor.

Clinical features

It is often asymptomatic but may cause recurrent and severe hemoptysis.

Investigations

- Chest x-ray shows round lesion with crescent of air between the ***fungal ball*** and upper wall of cavity. Aspergilloma may be multiple.
- Serum antibodies against aspergillus fumigatus are present.
- Sputum contains fungal hyphae.

Treatment

- Surgical removal in case of massive hemoptysis is the treatment of choice.
- Bronchial artery embolism is an alternative approach to the management of recurrent hemoptysis.
- Intracavitary instillation of antifungal drugs has been tried but with little success.



Aspergilloma in left upper lobe cavity. Aspergilloma demonstrated using conventional tomography. Rounded fungal ball (arrows) separated from the wall of the cavity by a 'halo' of air.

INVASIVE PULMONARY ASPERGILLOSIS

Invasion of previously healthy lung tissue by aspergillus fumigatus is uncommon but produces serious and fatal condition usually in immunocompromised patient due to disease or drugs. Spread of infection throughout the lung is very rapid with production of consolidation, necrosis and cavitation. The formation of multiple abscesses is associated with productive cough that is blood-stained.

Diagnosis should be suspected in patient with suppurative pneumonia not responding to antibiotics. Sputum stains show fungal element.

Treatment is amphotericin 0.25-1 mg/kg daily by slow i.v. infusion over 6 hours along with flucytosine 150-200mg/kg daily by mouth or i.v. infusion.

SARCOIDOSIS

It is a multi-system granulomatous disease of unknown etiology. It is associated with imbalance between subsets of T lymphocytes and other disturbances of cell mediated immunity.

The lesion is granuloma histologically similar to tuberculosis but there is no caseation.

CLINICAL FEATURES

Peak incidence in 3[rd] and 4[th] decades with female predominance. Onset may be acute or chronic.

Pulmonary manifestations

- Patient may be asymptomatic and first time diagnose when routine chest x-ray is performed that shows bilateral hilar and paratracheal lymphadenopathy (other causes of bilateral hilar lymphadenopathy are lymphoma, pulmonary tuberculosis and carcinoma of bronchus with malignant spread).
- The most common presentation is with respiratory symptoms such as persistent cough and dyspnea as a result of pulmonary infiltration and fibrosis causing interstitial lung disease. Pulmonary function tests show restrictive lung disease.

Extra-pulmonary manifestation

Lymph nodes

Hilar, paratracheal, mediastinal, cervical, axillary, epitrochlear, inguinal and mesenteric lymph nodes are enlarged.

Skin lesions (in 25% of cases)

- *Erythema modosum:* bilateral tender red nodules on the anterior surface of legs, more common in acute form and resolve spontaneously within 2-4 weeks.
- *Skin plaques:* purple raised lesion on face, buttocks and extremities.
- *Maculopapular eruption*: around the eyes and nose.
- *Lupus parino:* a chilblain – like lesion, nodular, purple, swollen, shiny lesions on the nose, cheeks, lips, ears, fingers and knees.
- *Clubbing* of finger-occasionally present.

Eye lesions (in 25% of cases)

Uveitis, blurred vision, photophobia may lead to blindness. Keratoconjunctivitis sicca may cause dryness of eye.

Upper respiratory tract

Nasal mucosa is involved in 20% of cases with nasal stuffiness. There may be involvement of tonsils, epiglottis and vocal cords causing hoarseness, stridor.

Other systems involvement

- Liver: hepatomegaly (in 20%)
- Spleen: splenomegaly (in 40%).
- CNS: facial palsy, papilloedema, hearing abnormalities.
- Bones: cysts in bone.
- Heart: heart block, cardiac failure and pericarditis.
- Endocrine: diabetes insipidus, pituitary dysfunction.

PRESENTATION OF SARCOIDOSIS	
• Asymptomatic – abnormal routine chest radiograph	• 30%
• Respiratory and constitutional symptoms	• 20-30%
• Erythema nodosum and arthralgia	• 20-30%
• Ocular symptoms	• 5-10%
• Skin sarcoids	• 5%
• Superficial lymphadenopathy	• 5%
• Other e.g hypercalcaemia, diabetes insipidus.	• 1%

EXAMINATION OF PATIENT WITH SARCOIDOSIS

- *Skin:* erythma nodusum on legs, face andbuttocks. Lupus perino on face.
- *Eyes:* yellow conjunctival nodules, papilloedema, uveitis,
- *Respiratory system:* signs of interstitial lung disease.
- Lymph adenopathy, hepatomegaly and splenomegaly
- *Joints*: for arthritis
- *CNS:* facial palsy
- *Pulse:* for arrhythmia

INVESTIGATIONS

X-ray chest

- Stage 1: bilateral hilar lymphadenopathy
- Stage 2: bilateral hilar lymphadenopathy and pulmonary infiltration.
- Stage 3: pulmonary infiltration without hilar lymphadenopathy.

Transbronchial biopsy

Transbronchial biopsy is the most useful investigation. Positive results are seen in more than 90% of cases showing non-caseating granulomas.. Bronchoalveolar lavage fluid shows increase in lymphocytes.

Biopsy of superficial lymph node or skin

Biopsy of other tissues such as palpable lymph nodes, skin lesion or salivary glands may be performed. It provides histological evidence of non caseating granulomas

RADIOGRAPHIC CHANGES IN SARCOIDOSIS

Stage I

Radiography shows bilateral hilar enlargement, usually symmetrical; paratracheal lymph nodes often enlarged.

Spontaneous resolution usually within one year in majority of cases. Often asymptomatic, but may be associated with erythema nodosum and arthralgia.

Stage II

Radiography shows a combination of hilar enlargement and pulmonary opacities which are often diffuse, but not always.

Patients usually asymptomatic. Spontaneous improvement occurs in majority.

Stage III

Radiography shows diffuse pulmonary shadows without evidence of hilar adenopathy. Evidence of pulmonary fibrosis may be present or develop.

Disease less likely to resolve spontaneously. Pulmonary fibrosis can cause breathlessness, pulmonary hypertension and cor pulmonale.

Serum angiotensin converting enzyme level

It is elevated in 40-80% patients with active sarcoidosis. However this test is neither sensitive nor specific enough for diagnosis. Serum angiotension converting enzyme level may be elevated in healthy person, primary biliary cirrhosis, atypical myobacterial infection, miliary tuberculosis, leprosy, and hyperparathyroidism.

Serum calcium

Hypercalcemia is present in 5% of cases while hypercalciuria in 20% of patients.

Tuberculin test

It is negative in 80% of cases.

Pulmonary function tests (PFTs)

PFTs reveal restrictive lung disease.

Blood CP/ESR

Blood CP shows leukopenia and ESR is elevated.

Kveim test:

The antigen (sarcoid tissue) is injected intradermally and a small nodule develops about 4 weeks later. This test is not performed now because of risk of transmission of disease.

Investigations in sarcoidosis

- Chest x-ray: bilateral hilar lymphadenopathy, lung infiltration.
- Transbronchial lung biopsy
- Biopsy of palpable lymph node, salivary gland or skin
- Serum angiotensin converting enzyme level
- Serum calcium
- Tuberculin test: mostly negative showing anergy
- CP: shows leukopenia

COMPLICATIONS

- Progressive lung fibrosis
- Bronchiectasis
- Lung cavitation
- Pneumothorax
- Hemoptysis
- Restrictive cardiomyopathy, arrhythmias and blocks.

MANAGEMENT

Stage I & II require no treatment

Stage III pulmonary sarcoidosis and sarcoidosis involving the extra-pulmonary organs needs treatment with prednisolone 20-40 mg daily for 4 weeks then maintenance dose 0.7-10 mg daily.

Indications of steroid therapy in sarcoidosis

- Constitutional symptoms
- Hypercalcemia
- Iritis
- CNS involvement
- Cardiac involvement
- Granulomatous hepatitis
- Skin lesion other than erythema nodosum
- Symptomatic pulmonary lesion

INTERSTITIAL LUNG DISEASE

The term interstitial lung disease is applied to a group of pulmonary diseases that have features in common as follows:

- Thickening of alveolar walls by edema, cellular exudates or fibrosis.
- Increased stiffness of the lungs (reduced compliance) associated with exertional dyspnea.
- Maldistribution of pulmonary ventilation and perfusion and a gas transfer defect leading to hypoxemia (particularly on exercise) hyperventilation and hypocapnia.

The onset is insidious; disease is usually chronic in duration. The initial insult is injury to the epithelial surface causing inflammation in the air spaces and alveolar walls creating an acute phase of alveolitis. Disease spreads to adjacent portions of the interstitium and vasculature and eventually produces fibrosis. The resultant scarring and distortion of lung tissue leads to significant derangement of gas exchange and ventilatory function.

ETIOLOGY

Causes of interstitial lung disease can be divided according to the known cause and unknown cause as in the following table:

CAUSES OF INTERSTITIALLUNG DISEASE (LUNG FIBROSIS)

Known cause

- Exposure to inorganic dusts such as silicosis, pneumoconiosis, beryllosis. And asbestosis.
- Drugs: methotrexate, amiodarone, hydralazine, busuphan and bleomycin.
- Radiation
- Aspiration pneumonia

Unknown cause

- Idiopathic pulmonary fibrosis (Cryptogenic fibrosing alveolitis)
- Connective tissue disease such as rheumatoid arthritis, SLE, scleroderma, ankylosing spondylitis and polymyositis.
- Eosinophilic pneumonias e.g. allergic bronchopulmonary aspergillosis.
- Sarcoidosis
- Amyloidosis
- Inflammatory bowel disease
- Biliary cirrhosis

IDIOPATHIC PULMONARY FIBROSIS

Idiopathic fibrosing alveolitis or idiopathic fibrosing interstitial pneumonia or Cryptogenic fibrosing alveolitis usually develops in late middle age and causes diffuse fibrosis throughout the lung fields.

PATHOGENESIS

Histologically there are two main features

- Cellular infiltration and thickening and fibrosis of the alveolar walls in the presence of neutrophils,
- There is variable degree of fibrosis and in most cases progressive fibrosis occurs. It has been suggested that release of oxidants from neutrophils, eosinophils, & macrophages cause tissue injury followed by fibrosis by the release of fibronectin and growth factors from alveolar macrophages.

CLINICAL FEATURES

Diffuse fibrosis throughout the lung fields presents with

Progressive exertional dyspnea accompanied with dry cough. There may be cyanosis which eventually leads to respiratory failure, pulmonary hypertension and corpulmonale.

On examination

- gross clubbing of fingers and toes
- Chest expansion is reduced
- Numerous bilateral end-inspiratory crepitations audible over the lower zones posteriorly.

INVESTIGATIONS

- *X-ray chest:* Diffuse pulmonary opacities most obvious in lower zones.
- The hemidiaphragms are high due to pulling effect of fibrosis and the lungs appear small.
- In advanced cases x-ray chest shows 'Honey-comb appearance" in which diffuse pulmonary shadowing interspersed with small cystic translucencies.

The main causes of honey-comb lung	
Localized	**Diffuse**
• Systemic sclerosis • Sarcoidosis • Tuberculosis • Asbestosis • Berylliosis	• Cryptogenic fibrosing alveolitis • Rheumatoid lung • Histiocytosis X • Tuberose sclerosis • Neurofibromatosis

High resolution CT scan

It has enhanced diagnostic accuracy and is more helpful in early stages when chest x-ray changes may be slight or absent showing ground glass appearance.

Pulmonary function tests

These show a restrictive ventilatory defect with proportionate reduction in FEV and VC.

Arterial blood gases

ABGs show hypoxemia with normal $PaCO_2$.

Broncho-alveolar lavage

It shows increased numbers of cells (particularly neutrophils).

Lung biopsy

Transbronchial biopsy is often of no help, open lung biopsy may be required for diagnosis.

DIFFERENTIAL DIAGNOSIS

Bronchiectasis and other causes of lung fibrosis.

CONDITIONS WHICH MIMIC INTERSTITIAL LUNG DISEASE	
Infection	**Malignancy**
• Viral pneumonia • Pneumocystis carini • Mycoplasma pneumoniae • Tuberculosis • Parasites, e.g. filariasis	• Leukaemia and lymphoma • Lymphatic carcinomatosis • Multiple metastases • Aveolar cell carcinoma
	• Pulmonary edema • Pulmonary hemorrhage • Aspiration

MANAGEMENT

- Treatment with corticosteroids is beneficial in about 30% of patients. A trial of prednisolone is indicated in most patients with progressive disease. Prednisolone 40-60 mg / day for 6-8 weeks. If it gives response then reduce the dose 5 to 10 mg daily and if there is no response then withdraw the drug over few weeks.
- Azathioprine or cyclophosphamide may be added if there is no response or there is relapse on reducing the dose of prednisolone.
- Oxygen
- Single lung transplantation is severe cases.

LOCALIZED PULMONARY FIBROSIS

Most common cause is tuberculosis.

Inspection:

- Retraction of affected side
- Decreased movement of the affected side of the chest.

Palpation

- Displacement of heart to the same side if there is fibrosis of lower lobe.
- Shift of trachea if fibrosis of upper lobe.

Percussion

- Impaired or dull note

Auscultation

- Bronchial breath sounds
- Vocal resonance increased
- Coarse crepitations

GENERALIZED PULMONARY FIBROSIS

In generalized fibrosis such as in interstitial lung disease chest movement is reduced on both sides, percussion note is normal, there is vesicular breathing, increased vocal resonance and end-inspiratory fine crepitations.

EOSINOPHILIC PULMONARY SYNDROMES

This is a group of disorders of different etiology in which lesions in the lungs produce a chest x-ray abnormality (usually opacities of consolidations) associated with an increase in the number of eosinophils in the peripheral blood (eosinophilia). Chest radiograph abnormalities clear rapidly when steroids are given that reduce eosinophil count.

PREDISPOSING FACTORS

Extrinsic (cause known; usually allergy to the following.

- *Parasites* : ascaris, toxocara, filaria.
- *Drugs:* Nitrofurantoin, para-aminosalicylic acid, sulphasalazine, imipramine, chlorpropamide, phenylbutazone, thiazides, tricyclic anti-depressants, isoniazid.
- *Fungi*: Aspergillus fumigatus (causing allergic bronchopulmonary aspergillosis

Intrinsic (cause unknown)

- Loeffler's syndrome
- Acute eosinophilic pneumonia
- Chronic eosinophilic pneumonia
- Churg- Strauss syndrome
- Hyper-esinophilic syndrome
- Polyarteritis nodosa

LOFFLER'S SYNDROME

It consists of acute eosinphilic pneumonia of unknown cause characterized by migrating pulmonary infiltrates and minimal clinical features.

ACUTE EOSINPHILIC PNEUMONIA

It is an idiopathic acute febrile illness of less than 7 day's duration with severe hypoxemia, pulmonary infiltrates, and no history of asthma.

CHRONIC EOSINOPHILIC PNEUMONIA

It presents with significant systemic symptom including fever, chills, night sweats, cough, anorexia and weight loss of several weeks to months duration. The chest x- ray classically shows peripheral infiltrates resembling a photographic negative of pulmonary edema. Dramatic clearing of symptoms and chest x-rays is often noted within 48 hours after initiation of corticosteroid therapy.

CHURG – STRAUSS SYNDROME

It is a multisystem vasculitic disorder that frequently involves the skin, kidney and CNS in addition of lung. The disorder occurs at any age and especially in patients with bronchial asthma. Patient presents with chronic asthma, pulmonary infiltrates, vasculitis and eosinophilia. The lung infiltrates may be patchy and responsive to corticosteroids. The disease is progressive and fulminating unless treated with corticosteroid therapy.

HYPER- EOSINIPHILIC SYNDROME

It is characterized by presence of over 1500 eosinophils per microlitre of peripheral blood for 6 months or longer and absence of evidence of parasitic, allergic, or other known cause of

eosinophilia. The heart may be involved with *tricuspid valve abnormalities* or endomyocardial fibrosis and a restrictive cardiomyopathy. Lung, liver, spleen, skin, and CNS are involved. Treatment is corticosteroids.

BRONCHOGENIC CARCINOMA

Bronchogenic carcinoma is the most common malignant disease. It is a common cancer in men and secondly in women (after breast cancer). Most patients are more than 50 years old.

RISK FACTORS

1. Cigaratte smoking – most important.
2. Industrial carcinogens.
   - Arsenic – glass workers
   - Asbestos – insulation, textile, asbestos, mining.
   - Coal dust – road work, coke oven workers
   - Ionizing radiations:
   - Chromium: Leather, ceramic, metal
   - Vinyl chloride: Plastic workers
3. Air Pollution
4. Existing lung damage – COPD, lung fibrosis.

PATHOLOGY

Classification according to the cell types:

- Squamous cell carcinoma 35%
- Adenocarcinoma 30%
- Small cell carcinoma 20%
- Large cell carcinoma 15%

Classification according to the location:

Centrally located

- Squamous cell carcinoma 70%
- Small cell carcinoma

Peripherally located

- Adenocarcinoma 30%
- Large cell carcinoma

Centrally located tumors that obstruct segmental, lobar or main stem bronchi may cause lung collapse as compared to peripherally located tumors that are diagnosed late.

CLINICAL FEATURES

Clinical manifestations of bronchogenic carcinoma are as a result of:

- Effects of tumor itself
- Features of local spread of tumor
- Features of metastasis
- Features of paraneoplastic syndromes

Symptoms due to tumor in the bronchus

- *Cough with sputum:* It is the most common early symptom. Sputum is purulent if there is secondary bacterial infection. The bronchial carcinoma itself does not produce sputum, but patients often have associated chronic bronchitis which is caused by cigarette smoking.
- *Hemoptysis:* Mostly in carcinoma of central bronchi but is less frequent in peripheral tumors. Repeated slight hemoptysis is common and characteristic feature.
- *Chest pain:* It is felt as fullness or pressure in the chest, however it may also be pleuritic due to invasion of pleura or ribs.
- *Breathlessness:* Owing to lung collapse resulting from obstruction of a large bronchus by the tumor or due to pleural effusion.

Frequency of common presenting symptoms of broncogenic carcinoma

- Cough 41%
- Chest pain 22%
- Cough and pain 15%
- Hemoptysis 7%
- Chest infection, shortness of breath, weight loss, malaise, hoarseness, distant spread and no symptoms <5% each.

Symptoms due to local spread

- *Pleura:* Chest pain due to malignant invasion of the pleura.
- *Esophagus* – dysphagia
- *Superior venacaval obstruction* – Producing morning headache, facial congestion and edema of the upper limbs. Dilated veins on the chest wall.
- *Erosion of rib* – Local & bony tenderness
- Pericardium – Cardiac tamponade

Nerves:

- Brachial plexus involvement – Pancost's syndrome comprising shoulder pain due to spread of carcinoma of the apex of the lung (Pancoast's tumor) to brachial plexus.
- Recurrent laryngeal nerve involvement causes hoarseness.
- Cervical sympathetic chain involvement in carcinoma of lung apex (pancoast's tumors) results in Horner's syndrome (combination of ipsilateral partial ptosis, miosis, anhydrosis of face and enophthalmos).
- Vagus – gastric symptoms.
- Intercostal nerves – Severe pain along the distribution of the nerve.

Symptoms due to Metastasis

- Fits & personality changes due to secondary deposits in the brain.
- Severe bone pain and pathological fractures due to bony metastasis
- Jaundice due to involvement of the liver.

NON-METASTATIC EXTRAPULMONARY MANIFESTATIONS (PARANEOPLASTIC SYNDROME)

- Anorexia and loss of weight
- Hypercalcemia due to release of parathyroid hormone – related peptide.
- Gynaecomastia due to release of human chorionic gonadotropin hormone.
- Cushing's syndrome: ectopic ACTH secretion causing Cushing's syndrome.
- Acromegaly: secretion of growth hormone releasing hormone causing acromegaly.
- Clubbing of the fingers
- In appropriate secretion of the ADH
- Hypertrophic pulmonary osteoarthropathy and tenderness in the wrist and ankle joints. X-ray of painful bones shows subperiosteal new bone formation.

Classification	Syndromes	Common cell type
Endocrine and metabolic	• Cushing's syndrome • SAIDH • Hypercalcemia	Small cell Small cell Squamous cell.
Connective tissue & bone	• Clubbing • Hypertrophic pulmonary ostecarthropathy	Squamous, adeno and large cell.
Neuro-muscular	Peripheral neuropathy Eaton-Lambert syndrome	Small cell

PARANEOPLASTIC SYNDROME			
Clinical syndrome	**Clinical features**	**Diagnosis**	**Management**
Hypercalcemia	Fatigue, confusion, anorexia, nausea, polyuria, weakness, constipation	• Serum calcium • Serum PTH	• 2-4 liter saline daily with frusemide. • Bisphosphonate • Calcitonin
Ectopic ACTH	Acromegaly	• GHRH • Insulin like growth factors • Glucose – suppressed growth hormone	• Bromocriptine • Surgical resection of tumors
Gynecomastia			Treatment of underlying cause

Physical signs in the chest

Commonly there are no physical signs unless significant bronchial obstruction or spread to the pleura or mediastinum.

- Finger clubbing (very rare in small cell carcinoma)
- Enlarged suprachlavicular lymph nodes.
- Superior vena caval syndrome manifesting as engorgement of jugular veins and then edema of face, neck and arms.
- Signs of collapse – if tumor obstructs a large bronchus.
- Fixed inspiratory rhonchi over a large bronchus due to obstruction.
- Signs of pleural effusion.
- Signs of pneumonia: due to infection beyond the obstruction may be present.

INVESTIGATIONS

Chest X-ray

Tumor mass needs to be between 1-2 cm in size to be recognized on chest x-ray reliably CT scan can identify tumors of small size.

COMMON RADIOLOGICAL PRESENTATIONS OF BRONCHIAL CARCINOMA.

- **Unilateral hilar enlargement**
  Central tumour, Hilar glandular involvement. Beware – peripheral tumour in apical segment of a lower lobe can look like an enlarged hilar shadow on the PA radiograph.
- **Peripheral pulmonary opacity**
  Usually irregular but well circumscribed. May have irregular cavitation within it. Can be very large.
- **Lung, lobe or segmental collapse**
  Usually caused by tumour within the bronchus causing occlusion. Lung collapse can be produced by compression of the main bronchus by enlarged lymph glands.
- **Pleural effusion**
  Usually indicates tumour invasion of pleural space: very rarely a manifestation of infection in collapsed lung tissue distal to a bronchial carcinoma
- **Broadening of mediastinum, enlarged cardiac shadow, elevation of a hemidiaphragm**
  Paratracheal lymphadenopathy may cause widening of the upper mediastinum. A malignant pericardial effusion will cause enlargement of the cardiac shadow. If a raised hemidiaphragm is caused by phrenic nerve palsy, screening will show it to move paradoxically upwards when patient sniffs.
- Rib destruction
  Direct invasion of the chest wall or blood-borne metastatic spread can cause osteolytic lesions of the ribs.

CT scan and MRI

- CT scan is particularly useful for identifying pathological changes in the mediastinum (e.g. enlarged lymph nodes and local spread of tumor and tumor metastasis detecting masses too small to be seen on x-ray.
- CT of brain and upper abdomen (liver, adrenals and periaortic lymph nodes) is required to detect metastasis. Bone x-rays and bone scan is required if metastasis is suspected.
- MRI may be safer than CT scan in evaluation of invasion of the mediastinum and chest wall by lung cancer (safety is because no dye required in MRI).

SOME CAUSES OF A MEDIASTINAL MASS

Superior mediastinum	Posterior mediastinum
Retrosternal goiter • Vascular lesion Persistent left superior Vena cava Prominent left subclavian artery • Thymic tumour • Dermoid cyst • Lymphoma • Aortic aneurysm **Anterior mediastinum** • Retrosternal goiter • Dermoid cyst • Thymic tumour • Lymphoma • Aortic aneurysm • Germ cell tumour • Pericardial cyst • Hernia through the diaphragmatic foramen of Morgagni	**Neurogenic tumour** • Paravertebral abscess • Oesophageal lesion • Aortic aneurysm • Foregut duplication **Middle mediastinum** • Bronchial carcinoma • Lymphoma • Sarcoidosis • Bronchoganic cyst • Hiatus hernia

SOME CAUSES OF A SOLITARY PULMONARY NODULE ON THE CHEST RADIOGRAPH

Common
- Primary bronchial carcinoma
- Ocalized pneumonia
- Tuberculosis
- Pulmonary infarction

Uncommon
- Solitary metastasts (breast, sarcoma, kidney, testis).
- Bronchial adenoma
- Arterio-venous malformations
- Foreign body.

Cytology

- Sputum and pleural fluid cytology to detect malignant cells. Cytological examination of expectorated sputum permits definitive diagnosis in up to 80% of centrally located tumors but less than 20% of peripheral nodules.
- Pleural fluid cytology reveals cancer in 40-45% of cases, while the pleural biopsy along with pleural effusion cytology establishes diagnosis in 80% of cases.
- Tissues for histology can be obtained by bronchoscopy, percutaneous needle aspiration, mediastinoscopy, lymph node biopsy or biopsy of other metastatic sites.

Fibreoptic Bronchoscopy

- To get biopsy of the tumor
- To find operability of tumor

Transthoracic fine-needle aspiration biopsy

This involves direct aspiration through the chest wall of peripheral lung lesions under X-ray or CT screening. Specimen can be obtained in 75% of peripheral lesions that can not be biopsed transbronchially. Complication is pneumothorax (in 25%) requiring chest lube.

Supraclavicular lymph node

This can provide definite diagnosis whenever enlarged lymph nodes can be palpated supraclavicular fossa.

CHARACTERISTICS OF DIFFERENT TYPES OF BRONCHOGENIC CARCINOMA

Squamous cell carcinoma

- Mostly arise centrally from proximal tracheobronchial tree.
- Clinical features develop early due to proximal location causing obstruction of bronchus, cough, hemoptysis, lobar or segmental lung collapse and postobstructive pneumonia
- It tends to metastasize to regional lymph nodes. Distant metastasis occurs relatively late.
- Sputum cytology is diagnostic in most cases (40-60%)
- Bronchoscopy to get biopsy and to see tumor extension
- Treatment: Surgery and radiotherapy, Chemotherapy is far less effective.

Adenocarcinoma

- Mostly arise in the periphery in the mucus glands of small bronchi, thus remain undetected until they have spread locally or distally.
- It tends to metastasize to distant organs e.g. brain and bones. Invasion of pleura and mediastinal lymph node is common.
- This is the commonest bronchial carcinoma associated with asbestos, and relatively more *common in non-smokers, in women and in the Far East.*
- Chest X-ray shows solitary peripheral module.
- Sputum cytology has low diagnostic value in the absence of pulmonary symptoms e.g. cough and hemoptysis
- Clubbing and hypertrophic pulmonary osteoarthropathy are more common than in squamous cell carcinoma.
- Response-to radiation and chemotherapy is poor.

Small cell carcinoma

- This centrally located tumor orginates from neuroendocrine cells (Kulchitsky cells)
- It is also known as oat cell carcinoma
- Risk factors are smoking and uranium mining
- It may be associated with many paraneoplastic syndromes.
- It is rapidly growing and highly malignant, average survival time 2-4 months in the absence of treatment.
- Chest X-ray shows hilar or perihilar mass
- Sputum cytology should be done
- It is only one of the bronchial carcinomas that respond well to chemotherapy.
- Response to chemotherapy and radiotherapy is better than other lung tumors and therefore standard therapeutic option, surgery is rarely performed because it is metastasized at the time of diagnosis.

Large cell carcinoma

- This peripheral located tumor is large and grows rapidly.
- Histologic examination shows large cells.
- Chest X-ray shows large masses.
- The response to radiation and chemotherapy is poor.
- Treatment is surgical

Bronchoalveolar cell carcinoma

- This arises from alveolar type 2 pneumocytes.
- The tumors presents in two forms (a) Localized solitary nodular lesion (b) diffuse alveolar process
- This is not related to tobacco smoking
- Chest X-ray shows solitary nodule or pneumonic lesions.
- Response to radiotherapy and chemotherapy is poor.
- Treatment for solitary nodular lesion is surgery.

TREATMENT

Curative treatment is surgical resection. Unfortunately the majority of the patients present with evidence of tumor spread at the time of diagnosis and can only be offered palliative therapy.

Surgical resection:

- Results of surgical resection are poor in small cell carcinoma.
- Few patients are suitable for surgery.

5-year survival rate after resection of squamous cell carcinoma can be as high 75% to stage I and 55% in stage II.

Contraindications to surgery

- Distant metastasis
- Mediastinal involvement
  - Esophageal involvement
  - Vocal cord paralysis
  - Vena cava obstruction
  - Involvement of trachea
  - Positive supraclavicular lymph node biopsy.
- Advanced age
- Poor respiratory function
- Small cell carcinoma

Radiotherapy

- Radiotherapy is of great value to relieve distressing complication e.g. superior venacaval obstruction or pain due to chest wall invasion.
- It is the treatment is of the choice, if the tumor is inoperable for reasons such as poor lung function.
- Small cell carcinoma is more susceptible to radiotherapy. Prophylactic radiotherapy to brain is also given in small cell carcinoma.

Chemotherapy

- In small cell carcinoma chemotherapy is combined with radiotherapy. Drugs used are intravenous vincristine, cyclophosphamide, doxorubicin or intravenous cisplatin and etoposide given every 3 weeks for 3-6 cycles.
- Chemotherapy is non-small cell carcinoma is not much effective however in unresectable non small cell carcinoma chemotherapy with cisplatin combined with radiotherapy is superior to radiotherapy alone. Response rate is more than 20%.

Laser therapy

This is good for destroying tumor tissue occluding major airways to allow reaction of collapsed lung.

PROGNOSIS

Very poor, less than 10% patients survive 5 years after diagnosis.

Rarer types of lung tumor

Tumour	Status	Histology	Typical presentation	Prognosis
Adenosquamous carcinoma	Malignant	Tumours with areas of unequivocal squamous and adeno differentiation	Peripheral or central lung mass	Stage-dependent.
Carcinoma tumour	Low-grade malignant	Neuro-endocrine differentiation	Bronchial obstruction, cough	95% 5-year survival with resection
Bronchial gland adenoma	Benign	Salivary gland differentiation	Tracheobronchial irritation/obstruction	Local resection curative
Bronchial gland carcinoma	Low-grade malignant	Salivary gland differentiation	Tracheobronchial irritation/obstruction	Local recurrence occurs
Hamartoma	Benign	Mesenchymal cells, cartilage	Peripheral lung nodule	Local resection curative
Bronchoalveolar carcinoma	Malignant	Tumour cells line alveolar spaces	Alveolar shadowing productive cough	Variable worse if multifocal

PLEURISY

This is the term used to describe pain arising from any disease of the pleura.

Causes

- Pneumonia, Tuberculosis
- Malignancy invading the pleura
- Pulmonary infarction
- Rheumatoid arthritis & SLE

Symptoms

Sharp localized pain made worse on deep inspiration, coughing and bending movements.

On examination

- Diminished movement of chest on affected side
- Breath sounds may be diminished on affected side.
- Pleural rub: a crackling sound at the end of inspiration and beginning of expiration localized usually to small area of the chest wall.

Management

- Bed rest.
- Treatment of underlying lung disease
- Analgesic e.g inj. Pethidine 50mg 1/M or Tab. Dolobid BD or Tab. Ponstan 2 TDS
- Syp. Actifed DM for cough three times daily

PLEURAL EFFUSION

Pleural effusion is an abnormal accumulation of fluid in pleural space as a result of excessive exudation or transudation from pleural surfaces.

CAUSES

For the diagnosis purpose pleural effusion can be divided into transudate and exudates as following:

Transudate

Proteins less than 3g/dl and LDH is < 200 i.u/dl, fluid/serum LDH ratio < 0.6, fluid/serum protein ratio <0,5 and specific gravity is < 1.016.

Transudate develops due to increased hydrostatic pressure or reduced oncotic pressure (due to hypoalbuminemia). It may be bilateral.

- Congestive cardiac failure (most common)
- Nephrotic syndrome
- Cirrhosis of liver
- Myxoedema (hypothyroidism)
- Constrictive pericarditis
- Meig's syndrome: Right sided pleural effusion due to ovarian tumours.

Exudates

Protein < 3g/dl and LDH is < 200 i.u/dl, fluid/serum LDH ratio > 0.6, fluid / serum protein ratio > 0.5 and specific gravity is > 1.016.

Exudate develops due to capillary leakage as a result of inflammatory process such as following:

- Bacterial pneumonia
- tuberculosis
- Carcinoma of the bronchus
- Pulmonary infarction
- Lymphoma
- Connective tissue disease
- Acute pancreatitis
- Uremia
- Empyema
- Hemorrhagic effusion
- Chylous effusion

Empyema

Empyema is an exudative pleural effusion caused by direct infection of the pleural space, causing the pleural fluid to appear purulent or turbid.

Hemorrhagic pleural effusion

It is a mixture of blood and pleural fluid. About 10,000 RBC per microliter are necessary to create blood-tinged pleural fluid, while 100,000 RBC per microliter make pleural fluid grossly bloody. In the absence of trauma grossly bloody pleural effusion suggests cancer or pulmonary embolism.

Chylous effusion

It is a milky in appearance due to accumulation of lymph in pleural space as a result of disruption of thoracic duct due to trauma or infiltration by carcinoma.

TRANSUDATE VERSUS EXUDATES

Test	Exudate	Transudate
Fluid LDH	> 200	< 200
Fluid/serum LDH ratio	> 0.6	< 0.6
Fluid / serum protein ratio	0.5	< 0.5
Specific gravity	1.016	< 1.016
Appearance	Cloudy viscous	Clear, thin non-clotting

CLINICAL FEATURES

Symptoms

- Dry cough and pleuritic pain may precede the development of effusion.
- Dyspnea: It is the only symptom related to effusion and the severity depends on amount & rate of collection of fluid.

On examination

Inspection

- Decreased chest movements on affected side
- There may be bulging on affected side.

Palpation

- Reduced chest expansion and chest movements.
- Displacement of trachea to the opposite side.
- Decreased vocal fremitus.

Percussion

Stony dull percussion note

Auscultation

- Diminished or absent breath sounds.
- Reduced vocal resonance.
- There may be bronchial breath sounds and egophony just above the fluid level when the large effusion compresses the lung.
- There is no pleural rub when effusion develops.

INVESTIGATIONS

X-ray chest PA view

Pleural effusion is detected on X-ray when 250 ml or more fluid is present while clinically on 500ml. It presents as:

Mild: Obliteration of costophrenic angle on the affected side.

Moderate: Uniform dense opacity with curved upper level, the concavity facing upwards with the highest point in the axilla.

Severe: If effusion is large, then inform opacity obliterates the lung field completely.

Loculated effusion

Pleural fluid may become trapped (loculated) by pleural adhesions, forming unusual collections along the chest wall or in the lung fissures. Shadows with a broad base on the chest wall that point inward toward the hilum are characteristic of loculated effusions.

X-ray chest lateral decubitus view

It can detect very small amount of fluid, lateral decubitus view is performed when there is doubt about the opacity whether it is fluid or consolidation. In case of free fluid it comes higher while opacity due to consolidation or loculated effusion does not change the position.

Ultrasound
It is helpful in differentiation between loculated effusion and tumor. It also differentiates pleural effusion from pleural thickening.

Pleural aspiration and pleural biopsy
Pleural aspiration is diagnostic as well as palliative to relieve the dyspnea. Pleural biopsy is always indicated whenever a diagnostic aspiration of pleural fluid is performed because it is more helpful for diagnosis as compared to pleural fluid alone.

Pleural aspiration is done through intercostals space (ICS) over the area of maximum dullness on percussion or where maximum opacity on x-ray is seen, usually 6^{th} ICS laterally or 8^{th} ICS posteriorly. 20ml is sent for culture & sensitively, 20ml for cytology and 10ml for D/R (biochemical examination and microscopy) for pH, glucose, protein, LDH and cell types e.g neutrophils (in bacterial infection), lymphocyts (in tuberculosis).

OTHER INVESTIGATIONS RELATED TO SUSPECTED UNDERLYING CAUSE.

Glucose
Low glucose level in pleural fluid (< 40 mg /dl or fluid / plasma glucose ratio < 0.6), is seen in rheumatoid arthritis malignant mesothelioma empyema and tuberculosis.

PH
Low PH of pleural fluid < 7.20 is seen in empyema, rheumatoid arthritis, tuberculosis, malignancy and esophageal rupture.

Blood Cell Count
RBC < 10000/dl pulmonary infarction, tumor trauma and pancreatitis
WBC > 20000 are seen in paraneumonic effusion, and empyema.

Cytology
Malignant cells are present in 60% of malignant effusion.

Gram staining and culture

AFB stain and culture
To detect M. tuberculosis

Complement
Total C3 and C4 in the pleural fluid are decreased in SLE and rheumatoid arthritis, also in carcinoma, pneumonia and tuberculosis

Rheumatoid factor > 1:320 in rheumatoid pleural effusion

Amylase
Increased pleural fluid amylase conc. in pancreatitis, pseudocyst of pancreas and esophageal rupture.

Chylous effusion
Increased triglyceride level > 100 mg/dl is seen in thoracic duct trauma, tumor (lymphoma) and tuberculosis.

MANAGEMENT

- Bed rest
- Treatment of under lying cause.
- Therapeutic aspiration to relieve breathlessness 750-1000cc fluid can be aspirated in one sitting. Aspiration of larger amounts may case pulmonary edema.

Indications for aspiration of fluid are:

- Large effusion upto clavicle
- Cardiac or respiratory embarrassment
- Secondary infection of effusion
- If effusion does not tend to get absorbed spontaneously even after anti-tuberculous treatment.

Transudate
Transudative pleural effusion generally responds to treatment of underlying condition, therapeutic pleural fluid aspiration is indicated only if massive effusion causes dyspnea.

Tuberculous pleural effusion
Prednisolone 20mg daily should be added to antituberculous therapy for 4-6 weeks. It promotes rapid absorption of fluid. Aspiration is required if there is large effusion causing dyspnea.

Post pneumonic pleural effusion:

1. Pleural effusion complicating pneumonia (also called parapneumonic effusion) may require diagnostic aspiration to ensure that an empyema has not developed.
2. In uncomplicated parapneumonic effusion, there is no pleural infection and the pleural fluid glucose and pH are normal. Such effusion is likely to resolve spontaneously and the chest tube drainage is not required.
3. In complicated parapneumonic effusion pleural fluid is either frank pus or has the potential to organize into a fibrous peel. Chest tube drainage is required if any of the following is present.
    - Fluid is frank pus or bacteria are present on Gram-stain.
    - Pleural fluid glucose is < 40mg/dl.
    - Pleural fluid pH is < 7.2 or LDH> 1000 units/L.

CHARACTERISTICS OF IMPORTANT EXUDATES				
Etiology	**Gross appearance**	**WBC**	**RBC**	**Glucose**
Uncomplicated parapneumonic effusion	Clear to turbid	5000-25,000 polymorphs predominant	< 5000	Equal to serum
Empyema	Turbid to purulent	25,000-100,000 polymorphs predominant	< 5000	Very low
Tuberculosis	Serous	5000-10,000 lymphocytes predominant	< 10,000	Equal to serum.
Malignant effusion	Turbid to bloody	1000-100,000 lymphocytes predominant	100-several hundred thousand	Equal to serum

Malignant effusion

Effusions caused by malignant infiltration of the pleural surfaces re-accumulate rapidly. To avoid the distress of repeated aspiration, one attempt should be made to obliterate the pleural space (*pleurodesis*) in patients who fail to respond to chemotherapy or mediastinal radiations. Chemical pleurodesis is usually performed by instilling talc (4-5 g in 50 ml saline) or doxycycline (500mg in 50-100ml saline) through chest tube after fluid drainage.which produce an inflammatory reaction and extensive pleural adhesions causing obliteration of pleural space.



Large left pleural effusion. When chest X-rays are taken in the upright position and there are no pleural adhesions a pleural effusion produces uniformly dense shadowing with a concave upper margin which extends up towards the axilla

PNEUMOTHORAX

Pneumothorax means air in the pleural space, making an air containing pleural cavity. Air may enter the pleural cavity through the chest wall, mediastinum or diaphragm or from a puncture of the visceral pleura covering the lung. The term spontaneous pneumothorax refers to the pneumothorax that is not due to trauma.

ETIOLOGY

Causes of pneumothorax may be divided into two major groups; spontaneous and traumatic pneumohthorax.

Spontaneous pneumothorax

The term spontaneous pneumothorax refers to the pneumothorax that is not caused by trauma and is divided into primary and secondary spontaneous pneumothorax as following:

- **Primary spontaneous pneumothorax**
  It occurs in the absence of an underlying disease due to rupture of subpleural apical blebs, usually in tall, thin men between the age of 20-40 years and is almost exclusively in smokers.
- **Secondary spontaneous pneumothorax**
  Secondary pneumothorax occurs as a complication of rupture of bullae in COPD and asthma. Rupture of cavity in tuberculosis, lung abscess and cystic fibrosis.

Traumatic pneumothorax

It results from penetrating injuries or as a complication of pleural fluid aspiration, pleural biopsy, bronchoscopy, and positive presence ventilation.

PATHOLOGY

Types

There are three types of spontaneous pneumothorax :

1. **Closed pneumothorax**: The opening in the lung is very small and rapidly heals, air is reabsorbed and thus allowing the lung to re-expand.

2. **Open-pneumothorax:** The opening remains patent and the pressure in the pleural space remains equal to that of the atmosphere both on inspiration and expiration, therefore lungs cannot re-expand. The term open pneumothorax is also applied to pneumothorax resulting from penetrating wound of the chest wall.

3. **Tension-pneumothorax:**The communication between pleura and lung persists but is small and acts as one-way valve which allows the air to enter the pleural space during inspiration and coughing but prevents it from escaping. Very large volume of air may be trapped in the pleural space and intrapleural pressure causes not only compression of the underlying deflated lung but also mediastinal displacement towards the opposite side with consequent compression of the opposite lung resulting in hypoxemia and inadequate cardiac output (circulatory failure). Tension pneumothorax usually occurs during mechanical ventilation, pulmonary infection and penetrating trauma. It is a medical emergency and pressure should be relieved with insertion of a large bore needle.

CLINICAL FEATURES

Symptoms

- The onset is usually sudden
- There is pain or a feeling of tightness in the affected side of the chest, may be aggravated by deep breathing
- Increasing dyspnoea and in severe cases cyanosis
- Closed spontaneous pneumothorax: Dyspnoea is not severe and lung re-expands gradually within 2-4 weeks.
- Open spontaneous pneumothorax: the dyspnoea is not severe but it does not improve (while it improves in closed type).
- Tension Pneumothorax: Dyspnoea is rapidly progressive and accompanied by central cyanosis, tachycardia, hypotension and respiratory failure.

On examination (important short case)

Inspection

- Diminished expansion on affected side
- Bulging on the side of pneumothorax
- Displacement of apex beat towards oppssite side.

Palpation

- Displacement of trachea to opposite side.
- Tactile vocal fremitus absent.

Percussion

- Hyper-resonance
- If on the left side, abolition of cardiac dullness
- Right sided pneumothorax lowers the upper level of liver dullness.

Auscultation

- Breath sounds diminished or absent
- Amphoric bronchial breath sounds may be heard.

INVESTIGATIONS

X-ray chest shows:

- Sharply defined edge of the deflated lung, especially on a film taken in expiration.
- There is complete translucency between this pleural line and the chest wall with no lung markings.
- Hydropneumothorax: a few patients have secondary pleural effusion that demonstrates a characteristic air-fluid level.
- Mediastinal displacement in tension pneumothorax.

MANAGEMENT

Small (< 15% of chest x-ray volume)
Asymptomatic or only slight breathless patient requires no treatment, just observation is required.

Medium (15-50% of x-ray volume) Large (>50%)
If patient is dyspnic percutaneous aspiration can be performed with a 16-gauge canulla attached to a 50 cc syringe and a three-way tap.

Chest tube drainage is required when the pneumothorax is > 50% or tension pneumothorax or recurrence after percutaneous aspiration. The chest tube should be removed 24 hours after the lung has fully re-inflated and bubbling stopped. Air leak persisting more than 3 days is unusual, therefore surgery should be planned if pneumothorax persists after 3 days.

Specific therapy e.g for tuberculosis should be started immediately.

Recurrent pneumothorax
Recurrent pneumothorax is that occurs more than twice, it should be treated with obliteration of pleural space by pleurodesis.

PULMONARY EMBOLISM

Pulmonary embolism results from emboli arising from thrombi in the venous circulation or right side of the heart. More than 90% of pulmonary emboli originate as thrombi in the deep veins of lower extremities. Most deep venous thrombi originate in the calves and some 80% of these spontaneously resolve without embolization. The remainder, propagate to the iliofemoral veins. Detachment of the propagating thrombus in these proximal veins allows a clot to migrate into the inferior vena cava and ultimately to the pulmonary vasculature, where it causes obstruction.

ETIOLOGY

- *Deep venous thrombosis (DVT)* in the iliofemoral veins. Other less common sites of thrombus formation are prostatic and pelvic veins.
- Except in IV drug abusers, pulmonary emboli generally do not originate in the upper extremities.

PREDISPOSING FACTORS
These are the factors that predispose to venous thrombosis in lower limb

Venous stasis

- Immobility (bed-rest, surgery, limb paralysis)
- Low cardiac output, varicose veins

Venous injury

- Trauma
- Intravenous cannulation

Increased coagulability
Malignant disease, drugs (e.g. oestrogens, oral contraceptives), dehydration, polycythemia, nephritic syndrome, ulcerative colitis.

Inherited cogulation defects
Antithrombin-III, protein S deficiency

Increasing age

RISK FACTORS FOR DEEP VENOUS THROMBOSIS FOLLOWING SURGERY

- Abdominal or pelvic surgery
- Prolonged surgery and general anaesthesia
- Old age
- Obesity
- Malignancy
- Prior deep venous thrombosis
- Coagulation disorders

PATHOPHYSIOLOGY

Massive embolus

Large embolus occludes proximal arteries and right ventricular outflow causing rapid decrease in cardiac output and right ventricular failure. The prominent features are those of vascular collapse e.g. hypotension, syncope.

Small / medium – sized emboli

Small and medium – sized emboli occlude segmental arteries, causing infarction of the segment (manifested as pleural chest pain and hemoptysis).

Multiple micro emboli

Large numbers of tiny emboli occlude the capillary beds of the lung. Due to collateral vascular supply there is no pulmonary infarction but there is insidious loss of the microvascular bed supplying the gas exchange units of lungs leading to pulmonary hypertension and right ventricular failure.

CLINICAL FEATURES

Massive pulmonary embolism

- Tachycardia, hypotension and shock – due to diminished cardiac output.
- Raised JVP, right ventricular gallop rhythm, widely split P2: due to pulmonary hypertension and right ventricular failure.
- Central cyanosis: due to disturbance of pulmonary ventilation and perfusion
- Tachypnea (most common sign)

Small / medium – sized emboli

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Incidence of symptoms and signs of angiographically proved pulmonary thromboembolism in 327 patients.

	%
Symptoms	
Chest pain	88
Pleuritic	(74)
Nonpleuritic	(14)
Dyspnoea	84
Apprehension	59
Cough	53
Hemoptysis	30
Sweats	27
Syncope	13
Signs	
Respiratory rate > 16 / min	92
Crackles	58
Loud P2	53
Pulse > 100/min	44
Temperature > 37.8 C	43
Phlebitis	32
Gallop	34
Diaphoresis	36
Edema	24
Mumur	23
Cyanosis	19

INVESTIGATIONS

General diagnostic studies

1. Arterial Blood Gases (ABGs)

- Generally shows decreased PO2, PC02 and increased pH.
- *Alveolar – arteriolar (A-a) oxygen gradient* is high that indicates presence of decreased gas exchange This can be easily calculated from ABG. Normal A-a gradient among patients without a history of pulmonary embolism or DVT makes the diagnosis of pulmonary embolism unlikely
- ABG normal in small / medium sized embolus unless embolus is very extensive.

2. Chest X-ray

It may be normal, suggestive finding includes:

Massive embolus:

- Oligaemia of affected lung field
- Abrupt vessel cut off
- Dilatation of the hilar pulmonary arterial trunk

Small / medium sized embolus

- Pleural effusion
- Opacities of consolidation
- Horizontal linear opacities
- A wedge – shaped consolidation in the middle or lower lobes is highly suggestive of pulmonary infarction and is known "Hampton's hump,"
- Elevation of hemidiaphragm

3 ECG

- Sinus tachycardia (most common)
- Classical pictures is $S_1Q_3T_3$. It means S wave
- In lead I, Q wave in head III with T inversion.
- Normal ECG in small medium embolus

4. Echocardiography

May demonstrate thrombus in right ventricular outflow or main pulmonary artery.

5. Plasma D- dimmer

It is a degradation product of fibrin in the presence of thrombus. D- dimmer is elevated in thromboembolism.

Specific diagnostic studies

Ventilation / Perfusion (V/Q) Scan

V/Q Scan should be done in all clinically stable patients with suspected pulmonary emboli. This scan is typically interpreted as following for the presence of a pulmonary embolism.

1. Normal
2. Low probability
3. Intermediate probability
4. High probability

- Normal V/Q scan rules out pulmonary embolism
- High probability scan is confirmatory for pulmonary embolism
- Low and intermediate probabilities require more investigations e.g. pulmonary angiography.

Evaluation of deep venous thrombosis

These tests may support a diagnosis of thromboembolic disease in patients in whom a V/Q scan is nondiagnostic (low or intermediate probability)

- Doppler ultrasound
- MRI
- Venography – standard test.

Pulmonary Angiography

It is a confirm test for diagnosis of pulmonary embolism. Angiography is performed in the following situations:

- When clinical features and noninvasive tests are not diagnostic.
- V/Q scan of low or intermediate probability
- This may be the initial diagnostic test in hemodynamically unstable patient
- This is required if any type of surgical procedure for prevention of recurrent thromboemboli is planned e.g. interruption of the inferior vena cava.

PREVENTION OF VENOUS THROMBOEMBOLISM

Avoid venous stasis

Calf muscle stimulation (during surgery)
Early mobilization and active leg exercises)
Graduated support stockings

Anticoagulants

Low dose heparin (or low molecular weight heparin) (e.g. 5000 units subcutaneously 8-12 hourly) low dose warfarin / coumadin (INR 1,2-1.5: 1) full dose i.v. heparin or oral warfarin for patients at high risk.

TREATMENT

MASSIVE PULMONARY EMBOLISM

Supportive care

- Oxygen: to correct hypoxemia
- Normal saline IV: for hypotension
- Dopamine: to raise blood pressure.

Anticoagulation

Heparin IV should be started soon based on the clinical suspicion of pulmonary embolism without waiting for definitive studies are obtained, unless there is an absolute contraindication for anticoagulation. Anticoagulation is not definitive therapy but a form of secondary prevention. It retards additional thrombus formation, allowing endogenous fibrinolytic mechanism to lyse the existing clot.

Dose of heparin

Heparin is given according to the weight; first in bolus form and then in infusion form.

- Initial loading dose: 80 units/kg/hour
- Maintenance dose: 18 units/kg/hour for 5 days

Repeat apt every 6 hourly in the first 24 hours and change the dose accordingly. Once in the therapeutic range (46-70 seconds) in two consecutive measurements then perform aPTT daily.

Dose adjustment based on apt results	
aPTT	What to do
<35 sec	Re- bolus with 80 units /kg, increase infusion by 4 units /kg/hr
35-45 sec	Re- bolus with 40 units /kg, increase infusion by 2 units /kg/hr
46-70 sec	No change
71-90 sec	Decrease infusion rate by 2 units/kg/ hr
>90 sec	Stop infusion for one hour, then decrease infusion by 3 units /kg/hr

Low molecular weight heparin may be used instead of standard unfractioned heparin. It is given subcutaneously once or twice daily. There is no need for coagulation monitoring (aPTT) as its effect is predicted according to the dosage.

- Enoxaprin(Clexane) 1.5 mg/kg once daily but single dose not exceeding 180 mg).
- Dalteparin (Fragmin) 200 units/kg once daily but single dose not exceeding 18000 units.

Complications of heparin

- *Immune mediated thrombocytopenia;* therefore frequent monitoring of platelet count in first 14 days. Thrombocytpenia is less frequent with low molecular weight heparin.
- *Hemorrhage*: especially in patients taking aspirin that also interfere the function of platelets, old age, renal insufficiency and previous GI hemorrhage. Hemorrhage is less frequent with low molecular weight heparin.

Oral anticoagulation

Warfarin 5-10 mg/d orally should be started with heparin (as it takes 5-7 days to become therapeutic) and continue for approximately 6 –12 months or indefinitely if risk factors are still present or thromboembolism is recurred. Usual maintenance dose is 2-15 mg/day.

Thrombolytic therapy

Systemic thrombolytic therapy with streptokinase or tPA hasten the lysis of pulmonary emboli. The use of thrombolytic therapy is controversial because it has not yet been shown to reduce mortality in patients of pulmonary embolism. Thrombolytic therapy should be considered for patients with acute massive embolism who are hemodynamically unstable despite heparin therapy and do not appear prone to bleeding.

Inferior venacaval interruption

If thrombolytics and anticoagulants are contraindicated or if the patient continues to have recurrent pulmonary embolism despite anticoagulation therapy, vena caval interruption is indicated by transvenous placement of Greenfield filter in the inferior vena cava just below the renal veins.

TREATMENT OF SMALL / MEDIUM SIZED EMBOLUS

- Pain relief
- Anti-coagulants

COMMONLY USED DRUGS IN RESPIRATORY DISEASES

Following are the commonly used brands of drugs. Pharmaceutical companies are invited for advertisement of their products.

Systemic beta- agonists

Short acting beta- agonists (3-4 times daily)

- T. Ventolin (Salbutamol) 2mg, 4mg, 4mg SR, 8mg SR (GlaxosSmithKline)
- Syp. Ventolin.
- Inj. Ventolin 0.5mg
- SR: Sustained Release

- T. Venex (Salbutamol) 2mg, 4mg (Pharmatec)
- T. Bricanyl (Terbutaline) 2.5mg
- Syp . Bricanyl
- Inj. Bricanyl 0.5mg

Long- acting beta- agonists (twice daily)

- Bambec (Bambuterol) 10mg, 20mg (Barett Hodgson)
- T. Bremax (Tulobuterol) 1mg, 2mg (Abbot)
- T. Meptin (Procaterol) 50 mcg (Otsuka).

Xanthines

- T. Theograd (theophylline) 350mg (Abbot)
- T. Theo-dur (theophylline) 200mg, 300mg
- T. Quibron T/SR (theophylline) 300mg (Squibb)
- T. Respro SR (theophylline) 20mg, 300mg (Searle)
- Syp. Etaphylline (theophylline) French Pharma
- T. Phylocontin (aminophylline) 225mg (AGP)

Leukotrine receptor antagonist

T. Singulair (Monteleukast) 5mg, 10mg (MSD)

Mast cell stabilizers

- T. Zatofen (ketotifen) 1mg (Novartis)
- T. Aria (ketotifen) 1mg (Highnoon)

Inhalers

Short acting beta- agonists

- Ventolin (salbutamol) inhaler
- Butovent (salbutamol) inhaler
- Venex (salbutamol) inhaler
- Bricanyl (terbutaline)inhaler

Long acting beta- agonist

Serevent (salmeterol) inhaler GlaxoSmithKline

Combinations of corticosteroids and beta- agonist inhalers.

- Ventide inhaler (salbutamol+ beclomethasone) GlaxoSmithKline.
- Clenil compositum – A ((salbutamol + beclomethasone) Chiesi.
- Pulmicort inhaler (Budesonide) Barrett Hodgson
- Azmacort inhaler (Triamcinolone) Aventis Pharma.
- Becotide (beclomethasone) low dose; GlaxoSmithKline
- Becloforte (beclomethasone) high dose; GlaxoSmithKline

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- Pulmonary function tests.
- Pleural biopsy
- Ventilation perfusion scan
- Medistinoscopy
- Bronchoscopy
- Arterial blood gases
- Pulmonary angiography
- CT scan chest

- **Surgical procedures**
- **Oncologists**: peoples have very little knowledge about good oncologists and hematologist, please inform about good oncologists.

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ENDOCRINE DISEASES 5

PITUITARY GLAND

Pituitary gland has two lobes anterior and posterior lobes.

Anterior pituitary gland secretes:
1. Growth hormone (GH)
2. Thyroid stimulating hormone (TSH).
3. Adrenocorticotropic hormone (ACTH).
4. Prolactin (PRL)
5. Luteinizing hormone (LH)
6. Follicle- stimulating hormone (FSH).

Posterior pituitary releases
Posterior pituitary has storage function. Some hormones produced by hypothalamus are stored in posterior pituitary and then are released from here:
1. Oxytocin
2. Antidiuretic hormone (ADH).

FEATURES OF PITUITARY HORMONES EXCESS AND DEFICIENCY

Hormone	Excess	Deficiency
TSH		Secondary hypothyroidism
ACTH	Cushing's syndrome	Secondary adrenocortical failure. (features of Addison's disease).
Prolactin	Galactorrhoea Amenorrhoea Hypogonadism	
FSH and LH		Hypogonadism and infertility. Males: Loss of libido, impotence, gynaecomastia and decreased frequency of shaving due to hair loss Females: oligomenorrhea or amenorrhea. In both sexes: loss of pubic and axillary hair.
Growth hormone	Acromegaly	In adults causes muscle weakness, lethargy and obesity
ADH		Diabetes insipidus

PITUITARY TUMORS

Pituitary tumors are the most common cause of pituitary disease; these are usually benign adenomas. Primary carcinoma of pituitary gland is rare, but a metastastic tumor from a primary breast, lung, or kidney may occur in the hypothalamus and produce pituitary function.

CLINICAL FEATURES

Clinical features depend on the following three factors:
1. The size of tumour in the pituitary gland & effect of that tumor on surround structures (local complications)
2. There may be hypersecretion of hormone.
3. There may be hyposecretion of hormones due to compression of normal tissue by the tumor.

Local complications

- *Upward extension:* compression of optic chiasma causing visual field defects.
- *Lateral extension* into cavernous sinus causing dysfunction of cranial nerve 3, 4 and 6.
- *Stretch of dura mater* causes headache which is the most constant but least specific symptom.
- Interruption of CSF flow causing *hydrocephalus.*

Increased hormone secretion

- Acidophilic adenomas usually secrete excessive growth hormone that leads to *acromegaly or gigantism.*
- Basophilic adenomas usually cause excessive ACTH secretion that leads to *Cushing's disease and Nelson's syndrome.*
- Chromophobe adenomas, they are also called prolactinomas, secrete excessive amount of *prolactin.*
- Non-functioning adenomas: tumors that do not cause clinically apparent excess hormone secretion are called non-functioning adenomas (they are usually chromophobe adenomas).

Decreased hormone secretion

- Short stature due to growth hormone deficiency due to congenital defect of pituitary gland.
- Panhypopituitarism.

INVESTIGATIONS

1. X-ray skull (lateral view) may show enlargement of the sell turcica.
2. Perimetry for visual field that usually shows upper temporal quadrantnopia or bitemporal hemianopia.
3. Magnetic resonance imaging (MRI)
4. Serum hormone levels if deficiency or excess is suspected.

MANAGEMENT

Medical therapy

- Dopamine agonist such as bromocriptine reduces the size of macroedenomas.
- Growth hormone secreting tumors may respond to octerotide.

Surgical therapy

Trans-sphenoidal adenomectomy

Radiotherapy given after operation to reduce the incidence of recurrence.

CHARACTERISTICS OF COMMON PITUITARY AND SIMILAR TUMORS

Tumor or condition	Usual size	Most common clinical presentation
Prolactinoma	Most < 10 mm (microprolactinoma)	Galactorrhoea, amenorrhoea, hypogonadism, impotence
	Some > 10 mm (macroprolactinoma)	As above plus headaches, visual field defects and hypopituitarism
Acromegaly	Medium→large (>90 of skull X-rays abnormal)	Change in appearance, visual field defects and hypopituitarism
Cushing's disease	Most small (some cases are hyperplasia)	Central obesity, chance observation (local symptoms rare)
Nelson's syndrome	Often large	Post-adrenalectomy, pigmentation, sometimes local symptoms
Non-functioning tumors	Often large	Visual field defects; hypopituitarism; small ones often found at postmortem
Craniopharyngioma	Often very large and cystic (skull X-ray abnormal in >50%; calcification common)	Headaches, visual field defects, growth failure: (50% occur below age 20: about 15% arise from within sella)

THERAPEUTIC MODALITIES FOR HYPOTHALMIC AND PITUITARY TUMORS

	Surgery	Radiotherapy	Medical	Comments
Non-functioning pituitary macroadenoma	++	+	-	
Prolactinoma	+	+	++ Dopamine agonists	Dopamine agonists cause macroadenomas to shrink
Acromealy	++	+	+ Octreotide+ Dopamine agonists	Octreotide does not cause macroadenomas to shrink
Cushing's disease	++	+	-	Radiotherapy is used in children and to prevent Nelson's syndrome
Craniopharyngioma	++	+	-	
++First-line therapy: +second-line therapy				

HYPOPITUITARISM

ETIOLOGY

The causes of hypopituaritism are best classified on the basis of whether the lesion is in hypothalamus or in pituitary gland.

Hypothalamus

1. Congenital isolated deficiency of pituitary hormones (Kallmann's syndrome)
2. Acquired
   - Craniopharyngioma
   - Tuberculosis
   - Head injury, surgery
   - Radiotherapy
   - Tuberculosis, sarcoidosis, histocytosis
   - Syphilis
   - Encephalitis
   - Primary or secondary tumor

Pituitary

1. Pituitary tumors. Chromophobe adenoma (commonest cause)
2. Surgery, radiotherapy, head injury
3. Post-partum necrosis (Sheehan's syndrome)
3. Autoimmune.
4. Hemorrhage in pituitary tumor(apoplexy).

CLINICAL FEATURES

Congenital defects of hypothalamus: thee is an isolated failure of production of releasing hormone e.g. gonadotrophin releasing hormone causes failure of LH & FSH production and hence failure of sex hormone production. The condition is mostly associated with anosmia. Congenital defects usually present with short stature.

Pituitary lesion (esp. pituitary tumor): there is sequence of loss of pituitary hormones as following:

Growth hormone loss:

Growth hormone is usually the earliest to be lost, it presents as lethargy, muscle weakness, and increased fat mass but these features are not much obvious in adults.

FSH and LH loss:

It s the second hormone to be lost, it results in failure of sex hormones production) manifesting as:

- Loss of libido, and importance in male and oligomenorrhoea or amenorrhoea in female.
- Later gynaecomastia and decreased frequency of shaving.
- Axillary and pubic hair become decreased or even absent in both sexes.
- Wrinkled dry skin.

ACTH loss:

- ACTH loss results in cortisol deficiency, producing symptoms of secondary adrenal insufficiency (hypotension, hypoglycemia & nausea & vomiting).
- Skin pallor due to lack of melanin in the skin (in contrast to primary adrenal insufficiency in which hyperpigmentation occurs).

TSH loss

TSH loss causes secondary hypothyroidism (hypothermia, low metabolic rate, dry skin, constipation). *Frank myxedema is not seen* in secondary hypothyroidism.

Coma:

Patient with untreated severe hypopituitarism eventually goes into coma especially after some infection or injury.

COMA IN PATIENT WITH HYPOPITUITARISM

Possible cause	Measure	Etiology
Hypoglycemia	Blood glucose (low)	Lack of GH
Water intoxication	Electrolytes (Na, K, urea decreased)	Cortisol required for excretion of water load
Hypothermia	Rectal temperature (may be 32oC)	Hypothyroidism

INVESTIGATIONS

1. **X-ray skull:** may demonstrate enlargement of sell turcica due to tumor and suprasellar calcification in craniopharyngioma.
2. **MRI scan of brain**

3. **Pituitary function tests:**
   - Testosterone
   - Cortisol or (ACTH) adrenocorticotrophic hormone.
   - Prolactin (PRL)
   - Plasma (FSH) follicle stimulating hormone, and (LH) luteinising hormone.
   - T,3 T,4
   - Growth hormone: growth hormone secretion is pulsatile and is commonly undetectable; therefore some stimulatory tests are performed such as post- exercise sampling, insulin – induced hypoglycemia however arginine growth hormone releasing hormone stimulation test is more suitable.

MANAGEMENT

Treatment of underlying cause: if possible e.g. surgical removal of pituitary adenoma or carniopharyngioma.

Replacement therapy according to the deficiencies demonstrates is always necessary.

Cortisol replacement
Cortisol: 20mg on waking and 10mg at 6 p.m.

Thyroid replacement
Thyroxin 0.1-0.5 mg once daily.
This is dangerous to give thyroid replacement to patients with adrenal insufficiency without first giving glucocorticoid therapy.

Sex hormone replacement
Male – Depot testosterone esters (Sustanon) 250. 500 mg I/M every 2-4 weeks.

Female-cyclical estrogen therapy for three weeks with progesterone for days 14-12 in premenopausal females and human chorionic gonadotrophin I/M weekly in post-menopausal

Adrenal replacement:
Prednisolone 5-10mg daily

Growth hormone replacement
Recombinant human growth hormone.

HYPERPROLACTINAEMIA

CAUSES OF ELEVATED PLASMA PROLACTIN

Physiological
- Stress
- Pregnancy
- Lactation
- Nipple stimulation

Drugs
Dopamine antagonists
- Antipsychotics (phenothiazines and butyrophenones) Antidepressants
- Antiemetics (e.g. metoclopramide, demperidone)

Dopamine-depleting drugs
- Reserpine
- Methyldopa

Estrogens
Oral contraceptive pill

Pathological
- Common
  Disconnection hyperprolactinaemia (e.g. non-functioning pituitary marcoadenoma).
- Primary hypothyroidism
- Prolactinoma
- Polycystic ovary

Uncommon
- Hypothalamic disease
- Pituitary tumour secreting prolactin and growth hormone
- Renal failure

Rare
- Wet-nursing reflex (e.g. baby crying)
- Post-herpes zoster
- Ectopic source

CLINICAL FEATURES

1. Galactorrhoea and hypogonadism.
2. Unexplained infertility.
3. In women there is secondary amenorrhoea, oligomenorrhea or menorrhagia and anovulation with infertility.
4. In men there is decreased libido, erectile impotence, reduced shaving frequency and lethargy.

INVESTIGATION

1. **Plasma prolactin level.**
   - Normal upper level is 500 mU/L.
   - In pregnancy and lactation prolactin level may reach to 20000 mU/L.
   - In non- pregnant and non- lactating patients levels of 500-1000 mU/L are likely to be induced by stress or drugs.
   - Levels between 1000-5000 mU/l are likely to be due to drugs or microprolactinoma.
   - The levels above 5000 mU/l are highly suggestive of prolactinoma.
   - Unless the prolactin falls after withdrawal of relevant drug therapy, serum prolactin level > 1000/mU/L is an indication of MRI or CT scan of hypothalamus and pituitary gland.
2. **X-ray skull** to detect pituitary tumor.
3. **CT scan or MRI** of pituitary. MRI can detect all macroadenomas and about 70% of microadenomas also.
4. FSH, LH, TSH, and T4

TREATMENT

Medical
Dopamine agonist Bromocriptine (Tab. Parlodel) initially 1.25 mg at night & then progressive to 2.5 mg TDS orally for a long time. It can be stopped in some microadenomas after 10 years while in macroadenoma it should be continued until surgery or radiotherapy.

Surgical
Dopamine agonists not only lower the prolactin levels but also shrink the majority of prolactin-secreting macroadenomas. Surgery is required in macroadenoma, while microadenomas usually respond to dopamine agonist and no surgery is required. However microadenomas can be removed by transsphenoidal surgery in patients not responding to dopamine agonist or intolerant to it.

Radiotherapy:
Radiotherapy may be required for some macroadenomas to prevent re-growth if bromocriptine is stopped.

COMMON DIAGNOSTIC FACIES
- Acromegalic
- Thyrotoxic
- Myxedematous
- Cushinoid
- Pagestic (Paget's disease)
- Myotonic
- Parkinsonian
- Thalassemic
- Marfanoid
- Mitral

ACROMEGALY

It is a disease of adult life characterized by growth of bulk but not in length of bone especially of the extremities from over-secretion of growth hormone after epiphyseal closure, due to adenoma of anterior pituitary. Hypersecretion of growth hormone before puberty (before epiphyseal closure) produces gigantism. Most of the adenomas are macroadenomas (> 1cm in diameter).

Acromegaly is rarely caused by ectopic growth hormone – releasing hormone or growth hormone secreted by lymphoma, hypothalamic tumor, bronchial carcinoid or pancreatic tumor.

Growth hormone acts directly on some tissues, but most of its biological effects are because of stimulation of insulin-like growth factor (IGF-1) produced in the liver and other tissues.

- *ACROMEGALY IS VERY IMPORTANT TOPIC FOR MCQs.*

CLINICAL FEATURES

DUE TO LOCAL EFFECTS OF ADENOMA
1. Due to increased intrasellar pressure: Headache & vomiting
2. Due to pressure upon adjacent optic chiasma and nerves causing:
   - Bitemporal hamianopia
   - Cranial nerve palsy
   - Hemiparesis
3. Due to destruction of pituitary gland by the tumor:
   Hypothyroidism, impotence/ amonerrhoea

DUE TO PITUITARY HYPERSECRETION OF GROWTH HORMONE

Skeletal changes

- Large spade like hands & large feet.
- Enlargement of the lower jaw (prognathism)
- Prominent supraorbital ridges with large frontal sinuses.
- Increased hat size due to enlargement of sinuses and skull bones.
- Spacing apart of teeth
- Arthropathy
- Over growth of vertebral bone can cause spinal stenosis.

Soft tissue changes

- Tongue enlarged with difficulty in articulation. Hypertrophy of pharyngeal and laryngeal tissue causing obstructive sleep apnea.
- Thickening of lips and nose
- Thickening of soft tissue of hands & feet
- Thickening of skin, increased sweating, acne.
- Moist handshake (due to sweating of palm)
- Myopathy
- Visceromegaly e.g. cardiomegaly, thyroid goiter and hepatomegaly.
- Carpal tunnel syndrome.
- Colon polyps are common.

Metabolic effects

- Glucose intolerance (25%)
- Clinical diabetes mellitus (10%)
- Hypertension (50%)
- Weight gain due to increased mass of muscle and bone.
- Growth hormone secreting pituitary tumors usually cause hypogonadism due to secretion of prolactin or by suppression of normal pituitary tissue.
- Secondary hypothyroidism may occur.

COMPLICATIONS

- Hypopituitarism, hypertension, glucose intolerance or frank diabetes mellitus, cardiomegaly and cardiac failure.
- Carpal tunnel syndrome, arthritis of hips, knees, and spine, spinal cord compression.
- Visual field defects.
- Acute loss of vision or cranial nerve palsy may occur if the tumor undergoes spontaneous hemorrhage and necrosis called pituitary apoplexy.

INVESTIGATIONS

1. **Fasting serum prolactin and insulin – like growth factor 1 (IGF- 1).**
   IGF-1 is elevated while serum prolactin is also elevated in 30% of patients.

3. **Growth hormone level:** clinical diagnosis must be confirmed by measuring growth hormone levels during glucose tolerance test (GTT). Glucose 75g is given orally and serum GH is measured after 60 min. In normal subjects plasma growth hormone suppresses to below 2mU/l while in acromegaly it does not suppress and in about 50% of patient there is paradoxical rise.

4. Pituitary function tests: show partial or complete hypopuitarism.

5. **X-rays:** X- ray skull shows enlarged pituitary fossa & double floor may be seen due to greater enlargement of the gland on one side. X-rays of hand and feet may also show tufting of the terminal phalanges of fingers and toes. A lateral view of foot shows increased thickness of the heel pad.

5. **CT Scan & MRI** to detect tumor extent. MRI is superior to CT scan.

MANAGEMENT

Untreated acromegaly results in markedly reduced survival with most of the deaths from heart failure, coronary artery disease, hypertension and colonic tumors. The aim of therapy is to reduce growth hormone level below 5mU/L.

We have six choices:

1. Trans- sphenoidal surgery.
2. Trans- frontal surgery
3. Radiotherapy
4. Dopamine agonists
5. Octreotide
6. growth hormone antagonists

Surgical management

Endoscopic trans-sphenoidal surgery is the first-line therapy. Clinical remission occurs in 60-80% with pituitary microadenoma and 50%

with macroadenoma. Complications of surgery are infection, CSF leak and hypopituitarism. Hyponatremia may occur 4-13 days after surgery presenting with nausea, vomiting, headache or seizures.

- Trans-frontal surgery is rarely required only for very big tumors.

Radiotherapy:
Radiotherapy is a second – line treatment and is given if acromegaly persists after surgery and medical therapy. Growth hormone level falls slowly (over many years) and there is risk of hypopituitarism.

Medical management
Patients who fail to have clinical or biochemical remission after surgery are treated with somatostatin analogues or dopamine agonists.

Somatostatin analogues
Octreotide (Sandostatin) and lanreotide are synthetic analogue of somatostatin that lowers growth hormone but do not shrink the growth hormone producing tumor. Initially short acting octreotide is given as subcutaneous injection 2-3 times daily then replaced by long – acting intragluteal injection monthly. Side-effect is decreased gallbladder motility causing gallstone formation.

Dopamine agonists
Dopamine agonists are less potent in lowering growth hormone but are more effective in mixed growth hormone producing and prolactin producing tumors.
Bromocriptine (Parlodel) Dose: start from 1.25-2.5 mg/day & then gradually increase to 20-30 mg/day in divided doses. Side effects: nausea, vomiting, postural hypotension.

Growth hormone antagonists
Pegvisomant is a growth hormone receptor antagonist 20 mg subcutaneously daily is recently approved and is given to those patients in which growth hormone level cannot be reduced to safe levels with octreotide alone.

GIGANTISIM

Gigantism or excessive growth in height is due to excessive production of growth hormone from adenoma of anterior pituitary gland before epiphyseal closure. Height becomes 7-8 feet. Skeletal muscles may be powerfully developed but later pituitary insufficiency may occur with associated muscular weakness.

There may be hypertension due to excessive growth hormone.

- X-ray skull: shows enlargement of sella
- Treatment is same as of acromegaly.

CAUSES OF TALL STATURE
- Hereditary (both parents tall).
- Idiopathic
- Hyperthyroidism
- Chromosomal abnormalities: Klinefelter's syndrome, Marfan's syndrome.
- Metabolic abnormalities.

SHORT STATURE

CAUSES OF SHORT STATURE

With delayed puberty
- Constitutional / familial
- Systemic illness (e.g. asthma, malabsorption, celiac disease, cystic fibrosis, renal failure)
- Psychological stress
- Anorexia nervosa
- Excessive physical exercise
- Hypogonadism
- Turner's syndrome in girls
- Other endocrine disease (e.g. Cushing's syndrome, primary hypothyroidism, pseudohypoparathyroidism)

Without delayed puberty
- Isolated growth hormone deficiency
- Previous precocious puberty with closure of epiphyses (e.g. congenital adrenal hyperplasia, histiocytosis X, McCune-Albright syndrome)
- Prior problem restricting growth now resolved (e.g intrauterine growth restriction, congenital heart disease)
- Skeletal abnormality (e.g. achondroplasia, mucopolysaccharidoses).

INVESTIGATIONS

- Measure growth hormone.
- Measure testosterone (in boys) and estradiol (in girls).
- FSH, LH, thyroid function tests.
- Screening for systemic disease such as renal and liver function tests.
- Antigliadin and antimyosin antibodies for celiac disease.
- X-ray wrist for bone age.

MANAGEMENT

- Management is effective before puberty (before fusion of epiphysis).
- Hormone replacement if any deficiency.
- Small dose of estrogen in girls and testosterone in boys in case of constitutional puberty delay.

MALE HYPOGONADISM

Male hypogonadism may be primary (due to testicular failure) or secondary (due to failure of hypothalamus or pituitary).

ETIOLOGY

Primary hypogonadism

- Klinfelter's syndrome
- Autoimmune gonadal failure
- Mumps orchitis
- Hemochromatosis
- Tuberculosis
- Chemotherapy or irradiation
- Congenital adrenal hyperplasia
- Cryptochidism

Secondary hypogonadism

- Hypopituitarism
- Kallmann's syndrome
- Hyperprolactinemia

Androgen resistance syndromes

- Testicular faminisation syndrome
- 5α-reductase deficiency

CLINICAL FEATURES

Loss of libido, lethargy, muscle weakness, decreased frequency of shaving, gynaecomastia, erectile impotence, infertility or delayed puberty.

INVESTIGATIONS

- Serum testosterone level.
- FSH and LH (high in primary and low in secondary hypogonadism.
- Semen analysis
- Chromosomal analysis (karyotyping) to rule out Klinefilter's syndrome.

MANAGEMENT

- Testosterone replacement in primary hypogonadism
- FSH and LH in secondary hypogonadism.

CRYPTOCHIDISM

By the age of 5 years both testes should be in the scrotum, lack of descent (undescended testes) are more liable to trauma than if situated in scrotum. The semineferous tubules fail to develop in undescended testes and if the condition is bilateral sterility will follow. The interstitial cells can function normally producing testosterone and secondary sex characteristics may develop in the usual way.

Management

Human chorionic gonadotrophin (HCG) intramuscularly can induce descent in about 40% of children, but if failed or the condition is discovered in adulthood, then the testes should be either removed or placed in the scrotum surgically.

GYNAECOMASTIA

Presence of glandular breast tissue in males is called gynaecomastia (gynicomazia). It results from imbalance between estrogen and androgen, estrogen promotes while androgen opposes the breast tissue formation.

CAUSES OF GYNAECOMASTIA

Idiopathic

Physiological
- Neonates
- Peripubertal in adolescents
- Old age

Drug-induced
- Cimetidine
- Digoxin
- Spironolactone
- Anti-androgen therapies for prostatic carcinoma
- Some exogenous anabolic steroids, e.g. diethylstillbestrol

Hypogonadism

Primary
- Klinefelter's syndrome
- Autoimmune gonadal failure
- Mumps orchitis
- Haemochromatosis
- Tuberculosis
- Chemotherapy or infarction
- Rare forms of congenital adrenal hyperplasia

Secondary
- Hypopituitarism
- Kallmann's syndrome (GnRH deficiency)
- Hypoprolactinaemia

Androgen resistance syndromes
- Testicular ferminisation syndrome
- 5a-reductase deficiency

Estrogen excess
- Liver failure (impaired steroid metabolism)
- Estrogen-secreting tumor (testes, adrenal)
- Human chorionic gonadotrophin (HCG)-secreting tumors (testes, lung)----- one of my short case in FCPS was elderly man with gynaecomastia. Physical examination suggested carcinoma of lung (examiner agreed).

DIAGNOSIS

Take proper history especially drug history. Practically most of the patients with gynaecomastia are on drugs such as spironolactone for cardiac failure or cirrhosis of liver.
Perform serum testosterone, FSH, LH, estradiol, prolactin and HCG.

MANAGEMENT

Surgical excision by a plastic surgeon for cosmetic reason.

IMPOTENCE

Erectile failure or impotence is a common problem and most of the time related to anxiety, depression or as a complication of diabetes mellitus.

CAUSES OF IMPOTENCE

With reduced libido
- Depression
- Hypogonadism
- Hyperthyroidism, acromegaly, and Addison's disease.

With intact libido
- Anxiety
- Vascular insufficiency
- Neuropathic e.g. diabetes, alcohol excess, multiple sclerosis.
- Drugs: beta blockers, thiazide diuretics, antihistamines, metoclopramide, sedatives, tricyclic anti- depressants, antihypertensives.

Investigations
- Blood glucose
- Serum testosterone
- FSH, LH
- Serum prolactin.

Management
- Teststerone if there is hypogonadism.
- In diabetic neuropathy oral sildenafil (Viagra); a phosphodiestrase inhibitor is the first- line therapy. Nitrates are contraindicated with Viagra because of risk of severe hypotension.

- Injection of prostaglandin E1 by patient himself.
- Vacuum constriction device
- Penile prostheses

MALE INFERTILITY

A number of patients come to clinics with history of infertility and report of semen analysis in their hands advised by some general practitioner or gynecologist. We must be able to interprete the report of semen analysis and tell the patient about his status.

Primary infertility affects 10-15% of married couples. About 1/3 cases result from male factors, 1/3 from female factors and 1/3 from combined factors. Clinical evaluation is required following 6 months of unprotected intercourse. Ask about frequency and timing of intercourse (relate with female's menstrual cycle).

Oligospermia is the presence of less than 20 million sperms/ ml while azoospermia is the absence of sperm.

POSSIBLE CAUSES OF MALE INFERTILITY

Problem may be related to spermatogenesis, sperm motility, hypogonadism or impotence.

Testicular insults

- Testicular torsion
- Cryptochidism
- Trauma
- Varicocele

Infections

- Mumps orchitis
- Epididymitis

Environmental factors

- Excessive heat
- Radiation
- Chemotherapy

Drugs

- Anabolic steroids
- Cimetidine
- Spironolactone
- Alcohol
- Marijuana
- Sulfasalazine
- Ketokonazole
- Phenytoin

Systemic diseases

- Thyroid or liver disease
- Diabetic neuropathy
- Hernia repair: may damage vas defrns

EXAMINATION

- Scrotal examination for size and hydrocele.
- Palpate vas deferens, epidiymis,prostate.
- Look for features of hypogonadism such as lack of secondary sex characters.
- Look for systemic cause.

INVESTIGATIONS

Semen analysis

Seminal fluid analysis is performed on samples obtained by masturbation into a glass container after 24-36 hours of abstinence. Analysis should be performed within one hour. Normal values are as following:

- _Volume:_ 1.5 -6 ml. (seminal fluid volume less than 1.5 ml may result in inadequate buffering of the vaginal acidity and may be due to retrograde ejaculation or androgen insufficiency.
- _Liquefaction_ of seminal fluid in 15-30 min.
- _Motility:_ more than 60 % of sperm should be motile. Motility may be reduced from antisperm antibodies.
- _Morphology_: more than 60% sperms should be of normal morphology.
- _Sperm count:_ > 20 million/ml with a total count > 60 million per ejaculate.

Endocrinologic evaluation

It is required if history, examination suggests endocrinologic basis or sperm count is low.

Serum testosterone, FSH , LH and prolactin should be performed.

Scrotal ultrasound

To detect a subclinical varicocele.

TREATMENT

- Treatment of the cause.
- Replacement therapy if hypogonadism.

AMENORRHEA

Failure of menstruation or amenorrhea may be primary or secondary:

Primary amenorrhea: ameorrhea in a women who has never menstruated or failure of menarche by the age of 16, regardless of presence or absence of secondary sexual characteristics. It may result from congenital defects of uterus, cervix, vagina, ovarian failure or chronic anovulation.

Secondary amenorrhea: cessation of menstruation is called secondary amenorrhea.

CAUSES OF SECONDARY AMENORRHEA
Hypothalamic dysfunctions • Anorexia nervosa • Excessive exercise • Psychogenic
Pituitary disease Hyperprolactinemia
Ovarian dysfunction • Polycystic ovarian syndrome • Androgen- secreting tumors • Autoimmune (premature menopause) • Menopause
Adrenal disease • Cushing's syndrome • Congenital adrenal hyperplasia • Androgen- secreting tumors.
Thyroid disease Hypo- and hyperthyroidism
Other conditions Severe systemic disease e.g. renal failure, endometrial tuberculosis

Investigations

Serum FSH, LH, prolactin, estradiol and TSH should be checked.

Treatment

Treatment of the cause

HIRSUTISM

Hirsutism is the excessive hair growth in an androgen –dependent distribution in women (upper lip, chin, chest, back, lower abdomen, thigh, and forearm).

Virilization is the frontal balding, muscularity, clitromegaly and deepening of voice due to pronounced excess of androgen usually due to androgen secreting tumor.

CAUSES OF HIRSUTISM

Causes	*Clinical features*
Idiopathic	• Often familial • Mediterraneal or Asian background
Polycystic ovarian syndrome	• Obesity • Oligomenorrhoea or 2° amenorrhoea • Infertility
Congenital adrenal hyperplasia (95% 21-hydroxylase deficiency)	• Pigmentation • History of salt-wasting in childhood. • Ambiguous genitalia • Adrenal crisis when stressed • Jewish background
Exogenous androgen administration	Athletes
Androgen-securing tumour of ovary or adrenal cortex	Rapid onset Virilisation: clitromegaly, deep voice, balding, breast atrophy
Cushing's syndrome	Clinical features of Cushing's syndrome

INVESTIGATIONS

- Serum testosterone, FSH, LH , prolactin normal in idiopathic.
- *Cushing's syndrome:* over night 1 mg dexamethasone suppression test. Mild elevation of androgens.

- *Congenital adrenal hyperplasia:* elevated androgen. Abnormal rise in 17 OH-progesterone stimulated by ACTH.
- *Polycystic ovary synd:* LH: FSH ratio > 2.5:1, minor elevation in androgens and prolactin.

MANAGEMENT

- Underlying cause of hyperandogenism must be detected and treated if possible.
- Any drug causing hirsutism should be stopped such as minoxidil, cyclosporine, phenytoin, anabolic steroids, diazoxide and certain progestins.

For others:

- **Spironolactone** 50-100mg twice daily on days 5-25 of the menstrual cycle.
- **Finasteride** (Genesis 5mg) one tab. Daily.
- **Flutamide** (Flutamida Gador 250mg) daily with oral contraceptives.
- **Metformin (Glucophage)** 500-1000mg twice daily is effective in polycystic ovary syndrome.

Local treatment

Laser therapy is an effective therapy for facial hirsutism. Threading or epilation are alternatives.

POLYCYSTIC OVARY SYNDROME

It is common disorder affecting 2-5% women of reproductive life. These patients have a steady state of relatively high estrogen, androgen, and LH levels rather than the fluctuating levels seen in ovulating women.

Increased level of estrogen comes from obesity due to conversion of ovarian and adrenal androgen to estrone in body fat. High estrogen level suppresses FSH and causes relative increase in LH. Constant LH stimulation of ovary results in anovulation, multiple cysts, and theca cell hyperplasia with excess androgen production.

Common topic for MCQs

Clinical features

Polycystic ovary syndrome presents with:

- Hirsutism (70%)
- Obesity (40%)
- Virilization (20%)
- Amenorrhea (50 %)
- Abnormal uterine bleeding (30%)
- Normal menstruation (20%)
- Insulin resistance and hyperinsulinemia with increased risk of type 2 diabetes.
- Infertility (commonly)
- Increased risk of cancer of breast and endometrium due to unopposed estrogen production.

INVESTIGATIONS

- LH to FSH ratio > 2.5:1
- Increased androgens (testosterone and dehydroepiandrosterone sulfate (DHEAS).

MANAGEMENT

Weight reduction

Weight reduction to lower the conversion of androgen to estrogen to restore ovulation.

If the patient desires pregnancy

- Clomiphene plus dexamethasone for ovulation and to be pregnant.
- Metphormin 500mg three times daily if patient not responds to clomiphene and dexamethasone.

If the patient does not desire pregnancy

Medroxyprogesterone acetate 10mg/d for the first 10 days of month should be given to ensure regular shedding of endometrium so that hyperplasia will not occur.

For hirsutism

Spironolactone, dexamethasone or epilation or electrolysis.

DIABETES INSIPIDUS

Diabetes insipidus is characterized by the persistent excretion of excessive quantities of dilute urine and constant thirst. It can be divided into two types:

1. **Cranial**: due to deficient production of anti-diuretic hormone (ADH).
2. **Nephrogenic:** renal tubules unresponsive to ADH

CAUSES OF DIABETES INSIPIDUS

CRANIAL

Hypothalamic or high stalk lesion

- Craniopharyngioma
- Head injury, surgery
- Histiocytosis X
- Sarcoidosis
- Pituitary tumour with suprasellar extension
- Tuberculous meningitis, encephalitis, syphilis
- Metastases to pituitary

Genetic defect

- Autosomal dominant
- Autosomal recessive (DIDMOAD syndrome – association of diabetes inspidus with diabetes mellitus, optic atrophy and deafness)

Idiopathic

NEPHROGENIC

Genetic defect

Sex-linked recessive
Cystinosis

Metabolic abnormality

- Hypokalaemia
- Hypercalcaemia

Drug therapy

Lithium
Demeclocycline

Poisoning

Heavy metals

Caused by other disorders

- Pyelonephritis
- Renal amyloidosis
- Multiple myeloma
- Sjogren's syndrome

CLINICAL FEATURES

1. Polyuria & polydipsia
2. The patient may pass 5-20 or more liters of urine in 24 hours of very low specific gravity and osmolality. It is lethal unless the patient takes adequate fluids.

INVESTIGATIONS

1. High plasma osmolality, low urine osmolality.
2. ADH is not measurable in serum.
3. **Water deprivation test**: the object of this test is to establish the diagnosis of diabetes insipidus and to differentiate cranial from nephrogenic cause.
    - Diabetes insipidus is confirmed by a plasma osmolality > 300 mOsm/kg with a urine osmolality < 600mOsm/kg.
    - In cranial diabetes urine osmolality increases to >660 mOsm/kg after administration of desmopressin (an ADH analogue) while in nephrogenic diabetes insipidus there is no urine concentration after administration of desmopression.

TREATMENT

1. **Desmopressin** (an ADH analogue) is the treatment of choice for cranial diabetes insipidus and is given via the mucus membrane of the nose by spray. In sick patient it may be given by an intramuscular injection. In tablet form bioavailability is negligible.
2. **Thiazide diuretics** e.g. hydrochlorothiazide 50-100mg/d gets partial response in both cranial and nephrogenic diabetes insipidus.
3. Nephrogenic diabetes insipidus may respond to combination of indomethacin-hydrochlorothiazide or indomethacin amiloride.

ADRENAL GLAND

FUNCTION OF GLUCOCORTICOIDS

1. They increase blood glucose concentration by increasing gluconeogenesis and by decreasing glucose utilization.
2. They reduce protein stores of the body (protein catabolism) except those of liver.
3. They promote mobilization of fatty acid concentration and their utilization for energy.
4. They act as anti-inflammatory
5. They cause sodium retention

Function of mineralocorticoids

They regulate the electrolytes in extracellular fluid. They increase salt and water reabsorption from kidney, intestine, sweat glands and from saliva. Potassium loss occurs because potassium is secreted in exchange for sodium under influence of aldosterone.

PRINCIPAL FUNCTIONS OF ADRENAL HORMONES

Glucocorticoids

- Carbohydrate metabolism regulation (e.g. increase gluconeogenesis)
- Increase protein catabolism
- Immunomodulation
- Cardiovascular regulation (e.g. - increase blood pressure)

Mineralocorticoids

- Sodium retention (in distal nephron, sweat duct, colon, salivary gland)
- Potassium excretion

Catecholamines

- Increase heart rate
- Modulate vascular tone (vasoconstriction by noradrenaline) and vasodilatation by adrenaline)
- Antagonize insulin action

CAUSES OF ADRENOCORTICAL INSUFFICIENCY

Primary

- Addison's disease → ACTH ↑
- Corticosteroid biosynthetic enzyme defects → ACTH ↑

Secondary

- Hypothalamic or pituitary disease → ACTH ↓
- Withdrawal of glucocorticoid thera → ACTH ↓

ADDISON'S DISEASE
Primary adrenocortical insufficiency

Addison's disease is a primary adrenal insifficiency (i.e. disease affecting adrenal gland while the hypothalamus & pituitary gland are normal) in which there is destruction of the entire adrenal cortex resulting in deficiency of adrenocortical hormones (glucocorticoid, mineral corticoids and adrenal androgens).

In secondary adrenal insufficiency due to pituitary failure as a result of atrophy, tumor or necrosis minracorticoid production persists because it is under control of rennin- angiotensin system.

ETIOLOGY

Common

1. Autoimmune
2. Tuberculosis
4. Bilateral adrenalectomy
5. HIV

Uncommon

1. Metastatic carcinoma, lymphoma
2. Bilateral adrenal hemorrhage or infarction
3. Intra-adrenal hemorrhage (Waterhouse – Friedrichsen syndrome following meningococcal septicemia).
4. Hemochromatosis
5. Amyloidosis

CLINICAL FEATURES

They result from glucocorticoid usually together with mineral corticoid insufficiency, loss of adrenal androgen production and increased ACTH.

Presentation may be acute, chronic or acute on chronic as following:

Chronic presentation

Symptoms

Weakness, weight loss, nausea, vomiting, fever, anorexia, constipation, abdominal pain, impotence, depression, syncope due to postural hypotension, myalgia and mental irritability may be the presenting symptoms.

On examination

- *Hyperpigmentation*: hyperpigmentation often raises the suspicion. Hyperpigmentation is especially prominent over the knuckles, elbows, kness, posterior neck, palmar creases, buccal cavity and nail beds. New scars are also pigmented.
- *Hypotension and postural hypotension* are almost invariably present.
- *Vitiligo* is present in 10-20% of cases.
- Small heart, hyperplasia of lymphoid tissue and scanty axillary and pubic hair.
- Dehydration, general wasting.

Acute presentation

Many patients are not diagnosed in chronic phase and present with an acute adrenal crisis. Intercurrent disease, infection or surgery may be the precipitating factors.

Features include:

- Circulatory shock
- Hyponatremia
- Hyperkalemia
- Hypoglycemia (in some cases)
- Muscle cramps
- Nausea, vomiting, diarrhea
- Unexplained fever

INVESTIGATIONS

1. **Blood urea & serum electrolytes**
   - Urea raised
   - Sodium decreased
   - Potassium increased
   - Hypercalcemia
2. **Blood sugar**: low
3. **Blood CP:** neutropenia, lymphocytosis, eosinophilia
4. **X-ray chest**: may show tuberculosis, fungal infection or cancer as a possible cause.
5. **CT abdomen**: shows small non- calcified adrenals in autoimmune Addison's disease, enlarged adrenals in metastatic disease and calcified in tuberculosis (50%).. Calcification is also seen in adrenal hemorrhage, fungal infection, pheochromocytoma and melanoma.

Specific tests:

- **Serum cortisol:** serum cortisol <5 mg/dl at 8 AM is diagnostic especially if there is simultaneous elevation of plasma ACTH (usually >200 pg/ml).
- **ACTH stimulation test**: failure of plasma cortisol to rise following administration of ACTH.
- **Measurement of plasma ACTH:** a high level of ACTH with low or normal level of cortisol confirms primary hypoadrenalism.
- **Anti-adrenal antibodies** present in 50% cases of autoimmune Addison's disease.
- **Serum aldosterone:** is reduced with high plasma renin activity.

MECHANISMS OF FEATURES OF ADRENAL INSUFFICIENCY

Features of glucocorticoid insufficiency

1. Weakness, weight loss & malaise.
2. Anorexia, nausea, vomiting, diarrhoea or constipation.
3. Postural hypotension due to sodium loss.
4. Hypoglycemia.

Features of mineral corticoid insufficiency

Hypotension, hyponatremia, hyperkalemia

Features of increased ACTH secretion

Pigmentation of exposed areas & pressure areas e.g. elbow, knee, palmar creases, knuckles, mucous membrane, conjunctiva and recent scars.

Mechanism: the cause of pigmentation is that the decreased level of cortisol in blood has no feedback effect on ACTH. Therefore ACTH secretion continues from anterior pituitary gland along with melanin stimulating hormone (MSH), which is also secreted by the same cells that secrete ACTH, the increased MSH stimulates more melanocytes which produce melanin in excessive amount, resulting in pigmentation.

Features of adrenal androgen deficiency

Decreased body hair especially axillary and pubic hair.

TREATMENT

Glucocorticoid and mineralocorticoid replacement

Average replacement steroid dosages for adults with primary hypoadrenalism is as following :

Average replacement steroid dosages for adults with primary hypoadrenalism

Drug	Dose
Glucocorticoid	
Cortisol	20-25 mg daily e.g. 10 mg on waking, 5 mg at 1200h, 5mg at 1800h
Or	
Prednisolone	7.5mg daily 5 mg on waking, 2.5 mg at 1800h
Rarely	
Dexamethasone	0.75 mg daily 0.5 mg on waking, 0.25 mg at 1800h
Mineralocorticoid	
Fludrocortisone	50-400 μg daily
Androgens	
Dehydroepiandrosterone (DHEA)	50 mg orally each morning.

If tuberculosis is the cause of Addison's disease then antituberculosis chemotherapy should be given.

ADVICE TO PATIENTS WITH ADDISON'S DISEASE

Intercurrent stress
e.g. febrile illness – double dose of hydrocortisone

Surgery
- *Minor operation* – hydrocortisone 100mg by intramuscular injection with premedication.
- *Major operation* – hydrocortisone 100mg 6-hourly for 24 hours ® 50 mg i.m. 6-hourly.

Gastroenteritis
Must have parenteral hydrocortisone if unable to take by mouth

Steriod card
Patient should carry this at all times. Should give information regarding diagnosis, steroid, dose and doctor.

Bracelet
Patients should be encouraged to buy one of these engraved with the diagnosis and reference number.

ADRENAL CRISIS

(Acute adrenal insufficiency)

This is a medical emergency caused by sudden marked insufficiency of adrenocortical hormones.

Precipitating factors

- Stress: e.g. infection, trauma, surgery, prolonged fasting.
- Sudden withdrawal of adrenocortical hormone therapy in a patient with chronic insufficiency.

Clinical features

- Dehydration headache & confusion or coma may be present. Fever may be 105 ^{0}F or more.
- Nausea, vomiting, diarrhea & abdominal pain
- Sudden onset with fall of blood pressure (cold extremities, weak pulse, tachycardia)

Investigations

- Blood glucose – low
- Serum electrolytes – low sodium, high potassium
- Blood urea – high
- Blood culture: may be positive (usually meningococci)
- Urinry & blood cortisol levels – low.

Differential diagnosis

1. Diabetic coma
2. CVA
3. Acute poisoning
4. Other causes of confusion & coma
5. Other causes of high grade fever

Treatment

1. Inj. normal saline (and 5% dextrose if hypoglycemia) very fast.
2. Inj. hydrocortisone (Solu-cortef) 100mg I/V & then 100mg 6 hourly for two days & then shift the patient on oral prednisolone.
3. Antibiotics
4. Management of shock

Complications during treatment

1. Overhydration-producing pulmonary or cerebral edema
2. Hypokalemia – producing flaccid paralysis
3. Generalized edema & hypertension – due to excessive I/V fluids and corticosteroid.

SECONDARY HYPOADRENALISM

It may arise from hypothalamic – pituitary disease or from long-term steroid suppression. It can be differentiated from primary hypoadrenalism by the fact in secondary hypoadrenalism minerlocorticoid secretion remains almost normal because this is predominantly stimulated by angiotensin II.

HYPERALDOSTERONISM

Hyperaldosteronism may be primary or secondary

PRIMARY HYPERALDOSTERONISM

Etiology

- Adrenal adenoma
- Adrenal hyperplasia

Primary hyperaldosteronism due to adrenal adenoma is termed as Conn's syndrome.

Pathophysiology

Aldoseterone is secreted from zona glomerulosa of adrenal gland in response to stimulation by angiotensin II.

Following are the sequence of events

- The enzyme renin is secreted by the kidneys in response to decreased renal perfusion pressure or flow
- Renin causes formation of angiotensin I from angiotensinogen (an alpha 2 globulin)
- Angiotensin I is inactive but is converted to active form angiotensin II by converting enzymes.
- Angiotensin II causes power vasoconstriction & stimulation of aldosterone from adrenal gland.
- Aldosterone causes sodium retention and potassium loss, resulting in increase in blood pressure.

Clinical features

The usual presentation is with hypertension and hypokalaemia. The hypertension may be severe and associated with renal and retinal damage.

Investigations

- Serum electrolytes – hypokalaemia
- Urinary potassium loss over 30 mmol/day during hypokalaemia
- Plasma aldosterone – elevated & not suppressed with saline infusion
- CT Scan or MRI – for differentiation of adenoma from hyperplasia.

Treatment

- Adenoma – surgical removal
- Hyperplasia – aldosterone antagonists e.g. spironolactone 100-400 mg/day.

PRIMARY HYPERALDOSTERONISM

Etiology

- Unilateral adrenocortical adenoma (Conn's syndrome) 73%.
- Bilateral cortical hyperplasia (27%)

Clinical features

Hypertension, muscle weakness, paraesthesias, tetany, headache, polyuria and polydipsia.

Investigations

- 24- hour urine for aldosterone, cortisol and creatinine.
- Low plasma rennin with high 24- hr urinary aldosterone indicates hyperaldosteronism.
- Serum 18- hydroxycorticosterone > 85 μg/dl is seen in adrenal neoplasm.
- CT adrenals to localize the tumor.

Management

- Conn's syndrome: laproscopic adrenalectmy or lif e long spironolactone..
- Bilateral adrenal hyperplasia: spironolactone.

SECONDARY HYPERALDOSTERONISM

- Raised levels of aldosterone are present due to:
- Liver cirrhosis
- Nephrotic syndrome
- CCF with excessive diuretic therapy
- Malignant hypertension
- Unilateral renal ischemia

D/D from Conn's syndrome

In Conn's syndrome there is decreased renin level due to hyperaldosteronism while in case of secondary hyperaldosteronism there is increased renin level.

PHEOCHROMOCYTOMAS

These are rare tumors, 90% arise from adrenal medulla while 10% from elsewhere in the sympathetic chain. About 10% are malignant. Pheochromocytoma secretes catecholamine and is responsible for <0.1% cases of hypertension.

Clinical features
Some patients present with signs and symptoms of excessive catecholamine secretion while some present with complications of hypertension such as stroke, myocardial infarction, left ventricular failure or hypertensive retinopathy.

SYMPTOMS AND SIGNS OF PHAECHROMOCYTOMA

Symptoms	Signs
• Anxiety or panic attacks • Palpitations • Tremor • Sweating • Headache • Flushing • Nausea and/or vomiting • Weight Loss • Constipation or diarrhoea • Raynaud's phenomenon • Chest pain Polyuria	• Hypertension – intermittent or constant • Tachycardia • Arrhythmias • Bradycardia • Orthostatic hypotension • Pallor or flushing • Glycosuria • Fever • (Signs of hypertensive damage)

Investigations

- 24-hour urinary vallinylmandelic acid (VMA) or metanephrine and normetanephrine is a useful screening test. (These are the metabolites of adrenaline and noradrenaline).
- CT scan of abdomen for the localization of tumor.
- Scanning; useful for extra-adrenal tumors.

Management

Medical
Prepare the patient for surgery with alpha-blocker such as phenoxybenzamine 10-20 mg 3-4 times daily. If patient develops tachycardia, then combine beta blocker such as propranolol. Never give beta blocker first, because unopposed alpha activity can lead to severe hypertension.

Surgical
Tumor should be removed if this is possible, while patient should be prepared with 6 weeks course of alpha blocker.

MULTIPLE ENDOCRINE NEOPLASIA (MEN I AND MEN II)

Simultaneous occurrence of tumors involving a number of endocrine glands is called MEN.

MEN I (Werner's syndrome)

1. Primary hyperparathyroidism
2. Functioning pituitary tumours
3. Pancreatic tumours (e.g. insulinoma, gastrinoma)

MEN II (Sipple's syndrome)

1. Primary hyperparathyroidism
2. Medullary carcinoma of thyroid
3. Phaechromocytoma

CUSHING'S SYNDROME

Cushing syndrome is the term used to describe the manifestations of excessive corticosteroids due to any cause.

Cushing's disease is the term used when excessive corticosteroid secretion is due to increased ACTH as a result of pituitary adenoma. Cushing's disease is four times more common in females than in males.

ETIOLOGY

There are 2 main causes of Cushing's syndrome:

- **Iatrogenic** (chronic glucocorticoid therapy, e.g. for asthma, arthritis) is the most common cause.
- **Spontaneous**: causes may be ACTH dependent or independent as following:

ACTH-dependent

- Pituitary-dependent bilateral adrenal hyperplasia (i.e. Cushing's disease) in 43% cases of spontaneous Cushing's syndrome.
- Ectopic ACTH syndrome (e.g. bronchial carcinoid, small-cell lung carcinoma, pancreatic carcinoma) in 10%.
- Iatrogenic (ACTH therapy)

Non-ACTH-dependent

- Adrenal adenoma (in 32% of spontaneous)
- Adrenal carcinoma

Psdueo-Cushing's syndrome, i.e. cortisol excess as part of another illness

- Alcohol excess (biochemical and clinical features)
- Major depressive illness (biochemical features only, some clinical overlap)
- Primary obesity (mild biochemical features, some clinical overlap).

CLINICAL FEATURES OF CUSHING'S SYNDROME

Symptoms	(%)	Signs	(%)
Weight gain	91	Obesity	97
Menstrual irregularity	84	Plethora	94
Hirsutism	81	Moon face	88
Psychiatric	62	Hypertension	74
Backache	43	Bruising	82
Muscle weakness	29	Striae	56
		Muscle weakness	56

CLINICAL FEATURES

SYMPTOMS

1. **Weight gain:** owing to sal-water retention, it is the most common symptom.
2. **Muscle weakness:** due to increased catabolism of protein by excessive glucocorticoid. Quadriceps femoris are markedly affected. It becomes difficult or impossible to get up from squatting position (proximal myopathy)
3. **Backache**: due to excessive protein catabolism & osteoporosis of bone. Rib fractures are also common.
4. **Sexual disturbances:** Amenorrhea / oligomenorrhea in women and impotency in men.
5. **Depression or psychosis:**
6. **Hisutism:** excessive growth of male pattern hair in females.

SIGNS

1. **Obesity**: The distribution of flat is centripetal (like a *lemon on toothpicks).* Fat deposition over seventh cervical vertebra (buffalo hump) abdomen is protuberent and face is moon face. Characteristically the arms and legs are thin (truncal obesity).
2. **Hypertension and edema** due to salt-water retention.
3. **Plethora** (red cheeks), bruising, stria: stria are the pinkish stretch marks over the abdomen, buttock and thigh. Glucocorticoid excess leads to collagen break-down which result sin thinning of the skin and blood vessels resulting

in bruising, stria & plethoric appearance (red cheeks).
4. Acne and skin infections.
5. Muscle weakness due to excessive protein catabolism, wound healing is impaired.
6. Skin pigmentation – in ectopic ACTH producing tumors.
7. increased risk of opportunistic infections.

EXAMINATION OF PATIENT WITH CUSHING'S SYNDROME

(Long or short case)

General inspection

- Central obesity and thin limbs
- Skin bruising, atrophy
- Pigmentation of extensor areas

Arms

- Purple striae
- Proximal myopathy
- Hypertension

Mental state

- Depression
- Psychosis

Face

- Plethora, hisutism, acne
- Moon face
- Fundoscopy for signs of hypertension, diabetes
- Mouth-thrush

Abdomen

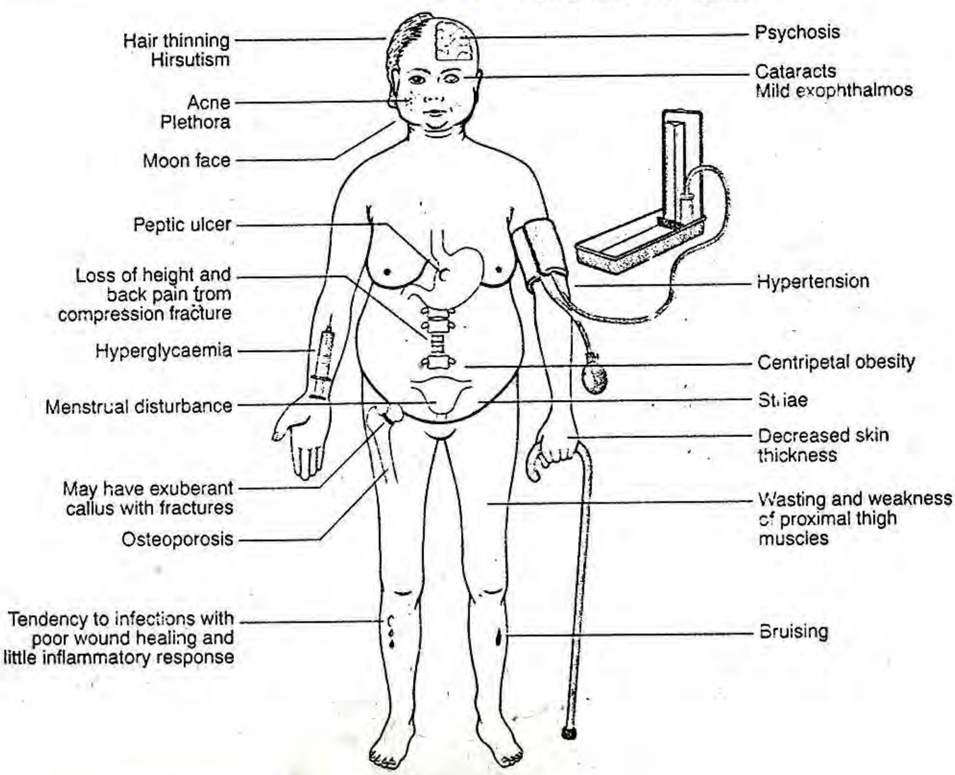
- Purple striae
- Adrenal masses
- Liver of metastasis

Back

- Bufallo hump
- Kyphoscoliosis (due to oseoporosis)
- Tenderness of vertebrae (due to osteoporotic fractures)

Legs

- Proximal myopathy
- Striae, bruises, edema



Cushing's syndrome: clinical features common to all causes.

INVESTIGATIONS

There are two phases of investigations

1. Confirmation of the presence or absence of Cushing's syndrome.
2. Differential diagnosis of its cause.

Confirmation

1. *Over night low dose dexamethasone suppression test*

   In normal subject cortisol level should be suppressed after taking dexamethasone due to feedback mechanism but in Cushing's syndrome feedback control is abnormal and there is no suppression of cortisol by dexamethasone.

   Dexamethasone 1mg is given at 11 p.m. and plasma cortisol is measured the following day at 8 a.m. A morning plasma cortisol level greater than 5μg/dl suggests hypercortisolism (Cushing's syndrome).

2. *24 hours urinary free cortisol measurment*: Urinary free cortisol is a reflection of free-cortisol in plasma and is a very useful index of increased cortisol secretion. Patients with Cushing's syndrome usually have urinary free cortisol levels between 300 to 1000μg/24 hours.

3. *48-hour low dose dexamethasone test:*

   If Cushing's syndrome is not confirmed on over- night low dose dexamethasone test, this test is performed. 0.5 mg 6-hourly for 48 hours; sample 24-hour urine cortisol and 9-hour plasma cortisol during second day.Urine free cortisol > 20μg/24 hours helps confirm hypercortisolism.

4. *Circadian rhythm:*

   In Cushing's syndrome there is characteristic loss of the circadian rhythm of plasma cortisol (i.e. instead of cortisol levels being lowest at midnight, they are about the same throughout the 24 hours.

   - Procedure: after 48 hours in hospital cortisol samples are taken at 9 hour and 24 hour. In Cushing's syndrome there is no variation of cortisol level & this called loss of circadium rhythm.

What is the cause of Cushing's syndrome

After confirmation of hypercortisolism (Cushing's syndrome) measurement of ACTH is done. In the presence of excessive cortisol secretion and undetectable ACTH indicates an adrenal tumor, therefore CT scan of adrenal gland is performed. If ACTH is normal or elevated, it indicates pituitary source (tumor) or ectopic ACTH syndrome. For pituitary tumor perform MRI while to detect ectopic source perform chest x-ray, CT chest and abdomen to find out the tumor.

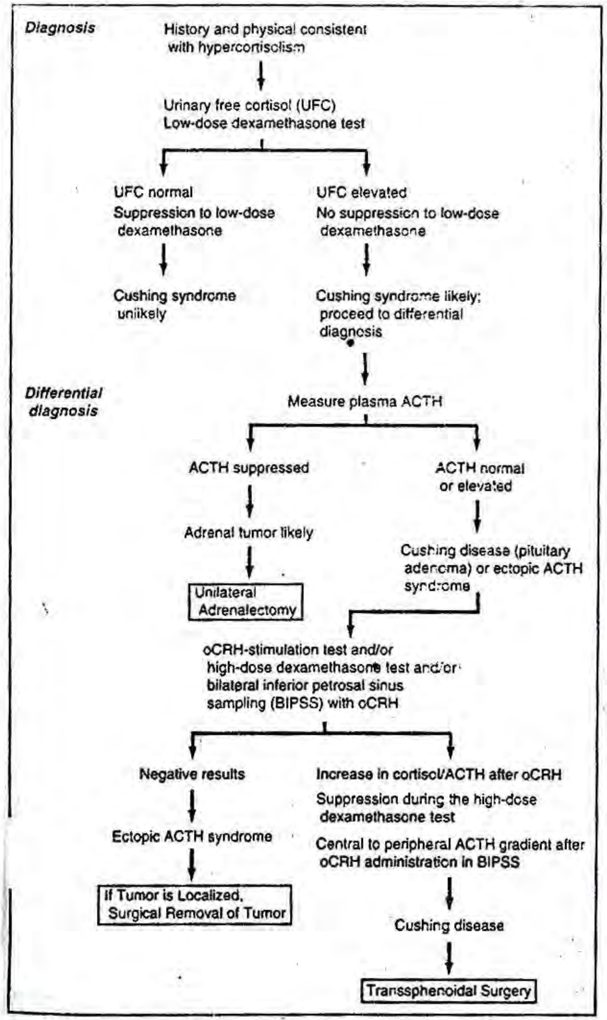
1. *Plasma ACTH level:*

   Very high level (above 300 mg/l) suggests the ectopic ACTH producing tumor (e.g. small cell carcinoma of bronchus)
2. *Adrenal CT scan*: to detect adrenal adenoma or carcinoma.
3. *Plasma K+* level is low in ectopic ACTH secretion.
4. *Corticotrophin releasing hormone test:* exaggerated ACTH reponses to exogenous corticotrophin – releasing hormone suggest pituitary dependent Cushing's disease.
5. *High dose dexamethasone test:* failure of urinary or plasma cortisol suppression suggest an ectopic source of ACTH or an adrenal tumor.

COMPLICATIONS

Treatment of Cushing's syndrome is necessary otherwise untreated patient may develop following serious complications:

- Hypertension and complications of hypertension.
- Diabetes mellitus and its complications.
- Increased risk of infection
- Ccompression fractures of osteoporotic spine.
- Aseptic necrosis of femoral head.
- Renal stones
- Psychosis.
- **Nelson's syndrome:** following bilateral adrenalectomy for Cushing's disease, a pituitary adenoma may enlarge progressively causing local destruction (visual field impairment) and hyperpigmentation; this complication is called Nelson's syndrome. *(common MCQ question).*



MANAGEMENT

CUSHING'S DISEASE

Trans- sphenoidal surgery

Selective trans- sphenoidal resection of pituitary adenoma is the treatment of first choice. Pituitary function returns to normal, however corticotrophs (e.g. ACTH) are suppressed and require 6-36 months to recover normal function. During this period hydrocortisone replacement therapy is necessary.

Bilateral laproscopic adrenalectomy

Patients who fail to have remission after pituitary surgery can be treated by laproscopic removal of both adrenal glands.

Radiotherapy

Radiotherapy has 23 % cure rate.

Medical treatment

Patients who are not candidate for surgery are given ketokonazole 200mg 6- hourly.

ADRENAL TUMORS

Adrenal tumors secreting cortisol are resected laproscopically. The contralateral adrenal is suppressed; therefore postoperative hydrocortisone replacement is required until recovery occurs.
Mitotane, ketokonazole or metyrapone can suppress hypercortisolism in unresectable adrenal carcinoma.

ECTOPIC ACTH PRODUCING TUMORS

They should be removed if possible, otherwise chemotherapy and radiotherapy may be used. Symptoms of Cushing's syndrome can be controlled with metyrapone or ketoconazole. Octreotide injection suppresses ACTH secretion in about 1/3 of such cases. Bilateral adrenectomy may be required.

PROGNOSIS

Five year survival of 95% and 10 year survival in 90% after successful surgery of benign adrenal adenoma and pituitary adenoma. If pituitary surgery is failed radiotherapy may be required. Prognosis of patient with ectopic ACTH secreting tumor depends on aggressiveness and stage of particular tumor. Patients with ACTH of unknown source have a 5 year survival rate of 65% and 10 year rate of 55%. Patients with adrenal carcinoma have a median survival of 7 months.

THERAPEUTIC STERIOD THERAPY

GLUCOCORTICOIDS

ACTIONS

Increases
1. Gluconeogenesis
2. Glycogen deposition
3. Protein catabolism
4. Fat deposition
5. Sodium retention
6. Potassium loss

Decreases
1. Protein synthesis
2. Host response to infection
3. Delayed hypersensitivity
4. Circulating lymphocytes & eosinophils

THERAPEUTIC USES

1. **Respiratory diseas**
   - Asthma
   - Chronic bronchitis and emphysema
   - Sarcoidosis
2. **Cardiac disease**
   - Post-myocardial syndrome
3. **Renal disease**
   - Nephrotic syndrome
   - Glomerulonephritis
4. **GIT**
   - Ulcerative colitis
   - Crohn's disease
   - Autoimmune hepatitis
5. **Rheumatological diseases**
   - SLE
   - Polymyalgia rheumatica
   - Temporal arteritis
   - Vasduclitis
6. **CNS**
   - Cerebral edema
7. **Skin diseases**
   - Eczema
   - Pemphigus
8. **Tumors**
   - Hodgkin's lymphoma
   - Other lymphomas
9. **Transplanation**

SIDE EFFECTS

CVS:
Hypertension, IHD, cardiac failure

GIT:
- Peptic ulcer exacerbation
- Pancreatitis

Renal:
- Polyuria & nocturia
- Renal stones

CNS:
- Change in mood and personality
- Depression
- Insomnia
- Psychosis, euphoria
- Benign intracranial hypertension

Endocrine
- Weight gain
- Diabetes
- Impaired growth
- Amenorrhoea
- Hirsutism
- Impotence

Muskuloskeletal
- Osteoporosis
- Proximal myopathy & wasting.
- Avascular necrosis

Eye
- Cataract
- Glaucoma

Metabolic
- Salt and water retention
- Hyperglycemia
- Hyperlipoproteinemia

Immunological
- Increased susceptibility to infection
- Lymphopenia
- Possible reactivation of tuberculosis.

PREVENTION OF SIDE EFFECTS

When corticosteroids are used for a long term basis then few steps can decrease the risk of steroid complications as following:

- Alondronate (bisphosphonate) 5-10 mg orally daily may prevent osteoporosis in patients taking steroids for a long time.
- Give calcium with vitamin D.
- Avoid prolonged bed rest that can increase muscle weakness.
- Vitamin A given after surgery for one week may improve wound healing.
- Watch for fungal skin infections
- Omeprazole for prophylaxis of peptic ulcer. Give steroids with meals.
- Hypokalemia may occur.
- When reducing dose ; watch for the signs of adrenal insufficiency due to glucocorticoid withdrawal.

COMPARISION OF COMMONLY USED NATURAL AND SYNTHETIC CORTICOSTEROIDS FOR GENERAL USE

Agent	Activity			Equivalent Oral Dose (mg)	Forms Available
	Anti-inflammatory	Topical	Salt-Retaining		
Short to medium – acting glucocorticoids					
Hydrocortisone (cortisol)	1	1	1	20	Oral, Injectable, topical
Cortisone	0.8	0	0.8	25	Oral, Injectable, topical
Prednisone	4	0	0.3	5	Oral
Presnisolone	5	4	0.3	5	Oral, Injectable, topical
Methylprednisolone	5	5	0	4	Oral, Injectable, topical
Mepredinisone	5		0	4	Oral, Injectable
Intermediate-acting gluocorticoids					
Triaminolone	5	53	0	4	Oral, Injectable, topical
Paramethasone	10		0	2	Oral, Injectable
Flupredinisolone	15	7	0	1.5	Oral
Long-acting glucocorticoids					
Betamethasone	25-40	10	0	0.6	Oral, Injectable, topical
Dexamethasone	30	10	0	0.75	Oral, Injectable, topical
Minerocorticoids					
Fludrocortisone	30	10	250	2	Oral, Injectable, topical
Desoxycorticosterone acteate	0	0	20		Injectable, pellets

HYPOTHYROIDISM

It may be primary from disease of thyroid gland or secondary to hypothalamic-pituitary disease.

ETIOLOGY

Primary hypothyroidism
It may be without goiter (in majority of cases) or with goiter as following:

Without goiter

- Idiopathic atrophy
- Radio-iodine therapy
- Agenesis (congenital)
- Transient due to thyroid hormone treatment withdrawn, subacute thyroiditis and postpartum thyroiditis.
- Patients with primary pulmonary hypertension have 22% incidence of hypothyroidism.
- Treatment with alpha- interferon

With goiter

- Hashimoto's thyroiditis
- Drug induced e.g. lithium, amiodarone, methimazole, propylthiouracil and sulfonamides.
- Endemic ioidine deficiency
- Inborn errors (genetic thyroid enzyme deficiency).
- Goitrogenic food due to iodine deficiency e.g. turnip.

Secondary hypothyroidism
Pituitary lesions

Tertiary hypothyroidism
Hypothalamic lesion

CAUSES OF HYPOTHYROIDISM	
Primary *Congenital* Agenesis Ectopic thyroid remnants *Defects of hormone synthesis* Iodinedeficiency Dyshormonogeneis Antithyroid drugsOther drugs (e.g. lithium, amiodarone, interferon) *Autoimmune* Atrophic thyroiditis Hashimoto's thyroiditis *Infective* Post-subacute thyroiditis	*Post-surgery* Post irradiation Radioactive iodine therapy External neck irradiation *Infiltration* Tumour *Peripheral resistance to thyroid hormone* **Secondary Hypothyroidism** Isolated TSH deficiency

Atrophic hypothyroidism
It is an autoimmune disorder & is the most common cause of hypothyroidism. It is associated with microsomal autoantibodies leading to lymphoid infiltration of gland and eventual atrophy and fibrosis. The ratio female to female is 6:1. Other autoimmune conditions such as pernicious anemia may be also present.

Hashimoto's thyroiditis
This form of autoimmune thyroiditis is associated with atrophic changes with regeneration, leading to goiter formation. The ratio of female to male is 6:1. It typically affects 20-60 year old female who presents with small or moderately large diffuse goiter. It may be associated with other autoimmune diseases such as myasthenia gravis, Sjogren's syndrome, adrenal insufficiency (Schmidt's syndrome), inflammatory bowel disease or celiac disease. It is commonly seen with hepatitis C. There are increased circulating levels of antithyroid peroxidase or antithyroglobulin antibodies.

Iodine deficiency
Usually in hill areas where the dietary iodine is insufficient, decreased thyroid hormone formation stimulates TSH that causes thyroid enlargement and goiter formation.

Dyshormonogenesis

This rare condition is owing to genetic defects in synthesis of thyroid hormone: patient develops hypothyroidism with goiter formation.

CLINICAL FEATURES OF HYPOTHYROIDISM	
General	**Haematological·**
• Tiredness	• Macrocystosis·
• Somnolence·	• Anaemia
• Weight gain·	• Iron deficiency (pre-menopausal women)
• Gold intolerance·	• Pernicious
• Hoarseness·	
• Goitre·	**Dermatological**
Cardiorespiratory	• Dry, flaky skin and hair, alopecia
• Bradycardia	• Purplish lips and malar flush
• Hypertension	• Carotenaemia·
• Angina	• Vitiligo·
• Cardiac failure	• Erytherma ab igne (Granny's tartan)·
• Xanthelasma·	• Myxoedema
• Pericardial and pleural effusion*	
Neuromuscular	**Reproductive**
• Aches and pains, muscle stiffness·	• Menorrhagia
• Delayed relaxation of tendon reflexes·	• Infertility
• Carpal tunnel syndrome	• Galactorrhoea
• Deafness·	• Impotence
• Depression	**Gastrointestinal**
• Psychosis*·	• Constipation·
• Cerebellar ataxia*·	• Ileus*
• Myotonia	• Ascites*

CLINICAL FEATURS

Early

- Symptoms may be fatigue, lethargy, weakness, arthralgia, myalgia, muscle cramps, cold intolerance, constipation, dry skin, headache, and menorragia.
- Physical signs may be few or absent. Signs may be thin brittle nails and hair, pallor and delayed reflexes.

Late

- Symproms may be slow speech, absence of sweating, constipation, peripheral edema, pallor, hoarseness, decreased sense of taste and smell, muscle cramps, dyspnea, weight gain and deafness. Amenorrhea or menorragia may be present.
- Physical signs may be goiter, puffiness of face and eyelids, typical carotenemic skin color, thinning of the outer halves of eyebrows, thickening of the tongue, hard pitting edema, effusion in peritoneal, pericardial and pleural cavities as well as in joints. Cardiac enlargement is usually due to pericardial effusion, heart rate is slow and diastolic hypertension may be present. Hyponatremia due to impaired renal tubular sodium reabsorption may be present.

EXAMINATION OF HYPOTHYROID PATIENT
(Long or short case)

Hands

- Peripheral cyanosis
- Swelling
- Dry cold skin
- Anemia

Arms

- Pulse: Bradycardia, small volume
- Test for carpal tunnel syndrome by tapping the flexor retinaculum medial to the base of thenar eminent with the wrist extended.
- Biceps reflex: delayed.
- Test for proximal myopathy (rare)

Face

- Alopecia, dry thin hair
- Mental slowness, depression
- Look for general swelling and periorbital edema
- Loss of outer halves of eyebrows
- Vitiligo
- Tongue may be swollen
- Check hoarseness of voice and slowness of speech by asking the name. (sometimes examiner says if you are allowed to ask one question from the patient for the diagnosis --- say I would like to ask the name of the patient to check hoarseness of voice).
- Test for deafness which may be bilateral and due to nerve involvement.

Legs

- Slow relaxation of ankle jerk
- Peripheral neuropathy
- Edema

Chest

- Pleural or pericardial effusion
- Rough sandpaper – like skin over the chest

INVESTIGATIONS

Thyroid function tests

- Serum T4 – low
- Serum T3: should not be measure because serum T3 concentration does not discriminate reliably between euthyroid and hypothyroid patients.
- Serum TSH – high (usually > 20 mU/l) in primary and normal or low in secondary hypothyroidism due to pituitary insufficiency.
- There are increased circulating levels of antithyroid peroxidase or antithyroglobulin antibodies in patients with Hashimoto's thyroiditis.

Other laboratory findings

- Serum lactate dehydrogenase **(LDH)** & creatinine kinase are raised.
- **Serum cholesterol** and triglyceride are raised.
- **Serum sodium** – decreased.
- **Anemia** with normal or increased MCV.

ECG: shows sinus bradycardia with low voltage complexes.

DIFFERENTIAL DIAGNOSIS

- Initially features of hypothyroidism are vague and commonly occurring even in non-hypothyroid persons therefore diagnosis may be missed. Hypothyroidism must be considered if patient presents with weakness, lethargy, myalgia, constipation, weight change, hyperlipidemia, and anemia.
- *Depression* and structural brain diseases may have been confused with hypothyroidism and should be in differential diagnosis.

COMPLICATIONS

- Coronary artery disease and cardiac failure due to hyperlipidemia.
- Increased susceptibility to infection.
- Megacolon.
- Myxedema madness: psychosis with paranoid delusions.
- Infertility (rare).
- Pregnancy in hypothyroidism often results in miscarriage. Babies born to hypothyroid mothers have IQ level less than normal.
- Myxedema coma.

Ask the patient about these complications in history taking.

MANAGEMENT

Replacement therapy with tab. Thyroxine available in 25, 50 and 100μg tablets.

- Start with 50μg/day for 1st 3 weeks.
- 100μg/day for next 3 weeks.
- 150μg/day further for the whole life.
- Thyroxine should be taken in the morning, avoid concomitant food and drugs that may interfere its absorption.
- Correct dose of thyroxine is that which restores serum TSH to normal
- In patients with ischemic heart disease the initial dose should be 25μg/day along with beta blockers and vasodilators. Over age 60 it should be started also with 25μg/day.
- Thyroxine should always be taken as a single daily dose as its half-life is approximately 7 days.
- Patient feels better within 2-3 weeks. Reduction in weight and periorbital puffness occurs quickly, but the restoration of skin texture takes 3-6 months.

Hypothyroidism and ischemic heart disease

About 5% patients of hypothyroidism develop IHD due to hyperlipidemia. They do not tolerate full thyroxine therapy and comlain aginal pain. In these patients coronary surgery (PTCA or by-pass) can be performed if patient not responding to beta-blocker and vasodilator.

Hypothyroidism and pregnancy

Pregnant women require 50μg more thyroxine than non-pregnant women. This is because during pregnancy there is increased serum thyroxine-binding globulin, therefore serum free thyroid hormone concentration decreases.

SECONDARY HYPOTHYROIDISM

This form is much less common than primary hypothyroidism and is characterized by atrophy of thyroid gland caused by failure of TSH secretion in patients with hypothalamic or anterior pituitary disease e.g. adenoma. It is commonly associated with other anterior pituitary hormones deficiency and there is clinical evidence of panhypopituitarism.

Pseudohypothyroidism

This is used to describe the inability to utilize thyroxine in tissue cells, despite normal thyroid function, leading to development of symptoms of hypothyroidism.

MYXEDEMA COMA

Myededema coma is a state of depressed level of consciousness or coma due to severe hypothyroidism, usually in elderly patients who appear myedematous. It is a medical emergency caused by hypothyroidism precipitated by acute illness or trauma.

S/S

1. Hypothermia
2. Hypoglycemia
3. Hyponatremia
4. Confusion of coma

Management

Thyroxine is not available for parenteral use, therefore:

1 T3 2.5-5μg I/V or orally 8 hourly until clinical improvement (after 48-72 hours) then start tab. Thyroxine 50μg/day.
2. Additional measure
   - Oxygen (if necessary)
   - Hydrocortisone 100 mg I/V 8 hoursly because patient should be assumed to be having secondary hypothyroidism due to hypothalamic or pituitary disease if there is no thyroidectomy scar or goiter is present.
   - 5% dextrose water to prevent hypoglycemia.
   - Broad-spectrum antibiotics.
   - Gradual re-warming by blankets.

HYPERTHYROIDISM

It is the clinical syndrome which results from exposure of the body tissues to excess circulating levels of free thyroid hormones. It is five times more common in females.

ETIOLOGY

1. Grave's disease – 76%
2. Multinodular goite – 14%
3. Autonomously functioning solitary thyroid nodule – 5%
4. Thyroiditis
   1. Subacute 3%
   2. Postpartum
5. Drugs : amiodarone

CLINICAL FEATURES

Hyperthyroidism develops usually insidiously and most patients have had symptoms for at least 6 months before presentation. The initial presentation may be to cardiologist for palpitation, dermatologist for pruritus, or gastroenterologist for chronic diarrhea. Atril fibrillation is uncommon in youngs but common in elderly. In children there may be behaviour disorders.

GRAVE'S DISEASE

This is the most common cause of hyperthyroidism and is an autoimmune process in which serum IgG antibodies bind to the thyroid TSH receptors and produce stimulation of thyroid hormone production, behaving like TSH. These antibodies are called thyroid – stimulating antibodies (TSAB). Most patients belong to age group 30-50 years.

Grave's disease is distinguished clinically from other causes of hyperthyroidism by the presence of:

- Diffuse thyroid enlargement (thyroid goiter).
- Ophthalmopathy (eye changes)
- Peritibial myxoedema (rare)

Most common symptoms of hyperthyroidism

1. Nervousness, irritability, tremor
2. Palpitation, dyspnea or exertion, angina
3. Weight loss, diarrhea
4. Increased sweating
5. Amenorrhea / impotence
6. Lid retraction and other eye symptoms in Grave's disease.
7. Heat intolerance, fatigue

CLINICAL FEATURES OF HYPERTHYROIDISM

Goitre
- Diffuse + bruit1
- Nodular

Gastrointestinal
- Weight loss despite normal or increased appetite
- Hyperdefacation (frequent bowel movement).
- Diarrhoea and steatorrhoea
- Anorexia
- Vomiting

Cardiorespiratory
- Palpitations, sinus tachycardia, atrial fibrillation
- Increased pulse pressure
- Ankle oedema in absence of cardiac failure
- Angina, cardiomyopathy and cardiac failure
- Dyspnoea on exertion
- Exacerbation of asthma

Neuromuscular
- Nervousness, Irritability, emotional lability, psychosis
- Tremor
- Hyper-reflexia, ill-sustained clonus
- Muscle weakness, proximal myopthy, bulbar myopathy
- Periodic paralysis (predominantly Chinese)

Dermatological
- Increased sweating, pruritus
- Palmar erythema, spider navi
- Onycholysis
- Alopecia
- Pigmentation, vitiligo
- Digital clubbing
- Peritibial myxoedema

Reproductive
- Amenorrhoea / oligomenorrhoea
- Infertility, spontaneous abortion
- Loss of libido, impotence

Ocular
- Lid retraction, lid lag
- Grittiness, excessive lacrimation
- Chemosis
- Exophalmos, corneal ulceration
- Ophthalmoplegia, diplopia
- Papilloedema, loss of visual acuity

Other
- Heat intolerance
- Fatigue, apathy
- Lymphadenopathy
- Thirst
- Osteoporosis

EXAMINATION OF HYPERTHYROID PATIENT (Long and short case)

General appearance
Hypo or hyperthyroid facies

Hands
- Warm and sweaty palms
- Tremor, onycholysis (separation of distal end of nail) also called Plummer's nail.
- Acropathy: clubbing and swelling of fingers.

Arms
- *Pulse:* tachycardia, irregular pulse due to atrial fibrillation, high volume collapsing pulse.
- Proximaly myopathy.
- Brisk reflexes

Eyes
- *Exophthalmos*: sclera visible below cornea.
- *Lid retraction*: sclera visible above cornea
- *Conjunctiva:* chemosis
- *Lid lag:* ask the patient to follow your finger descending at a moderate rate.
- The eye movements for *ophthalmoplegia*
- Examine fundi for *optic atrophy*
- *Proptosis*: look from behind and above.

Neck
- Look for thyroid enlargement, scar of surgery
- Palpate thyroid, auscultate for bruit
- Pemberten's sign: on raising the arm above head, patients with retrosternal goiter may develop signs of compression such as congestion of face, raised JVP and inspiratory stridor.

Chest
- Gynaecomastia in males
- Ejection systolic murmur
- Signs of cardiac failure

Legs
- Pretibial myxedema: bilateral firm, elevated dermal nodules and plaques which can be pink, brown or skin coloured caused by mucupolysaccharide accumulation.
- Hyperreflexia

COMPLICATIONS

- Atrial fibrillation
- *Periodic paralysis:* hypokalemic periodic paralysis in about 15 % of hyperthyroid patients presenting abruptly with paralysis often after oral carbohydrate (mostly patients correlate with biryani (rice) and sweat dish). Intravenous dextrose or vigorous exercise may be the precipitating factors. Attack lasts in 7-72 hours.
- Hypercalcemia and nephrocalcinosis.
- Osteoporosis
- Decreased libido, impotence, decreased sperm count and gynaecomastia may be noted.

INVESTIGATIONS

Thyroid function tests

- Serum TSH is low (< 0.05 mU/L).
- T3, T4 and free thyroxin are raised (T3 is more sensitive for hyperthyroidism because there are occasional cases of isolated T3 toxicosis).
- TSH receptor antibody levels are usually high in Graves' disease.
- Antithyroglobulin or antimicrosomal antibodies are usually elevated in Graves' disease.
- Serum ANA and anti- DNA are also elevated without evidence of SLE.

Thyroid radioactive iodine scan

It is performed in diagnosed case of thyrotoxicosis. High radioactive iodine uptake occurs in Graves' disease and toxic nodular goiter while uptake is low in subacute thyroiditis.

MRI

MRI of orbits is imaging method of choice to visualize Graves's opthalmopathy.

Other investigations

- Hypercalcemia
- Increased alkaline phosphatase
- Anemia, decreased granulocytes.
- Raised ESR in subacute thyroiditis.

DIFFERENTIAL DIAGNOSIS OF THYROTOXICOSIS

- *Acute psychiatric disorders*: T4 is elevated but TSH is normal.
- Exogenous thyroid administration.
- *Pheochromocytoma* (also presents with increased metabolism and weight loss).
- *Acromegaly* (it can also cause thyroid enlargement and tachycardia).
- Atrial fibrillation and angina refractory to treatment suggest the possibility of hyperthyroidism.
- *Other causes of exophthalmos*: orbital tumor, pseudotumor.
- *Other causes of opthalmoplegia*: myasthenia gravis.
- Thyrotoxicosis should be in D/D of muscle weakness and osteoporosis.

MANAGEMENT

Following are the three methods of treatment of hyperthyroidism:

1. Antithyroid drugs
2. Subtotal thyroidectomy
3. Radioactive iodine

Strategy
Anti- thyroid drugs are first tried for patients less than 40 years, if there is relapse then consider surgery.
Radioactive iodine may be given in patients more than 40 years and those who develop recurrence after surgery.

ANTI-THYROID DRUGS

Thioure drugs

- Carbimazole (Neo- Mercazole 5mg)
- Propylthiouracil

Mode of action

Thiourea drugs reduce the synthesis of new thyroid hormone by inhibiting the iodination of tyrosine.

Indications
First episode of hyperthyroidism in patient of less than 40 years of age, or patient with mild thyrotoxicosis, or fear of radioactive iodine.

Side effects

- Agranulocytosis (manifests as severe sore throat due to infection or unexplained fever). It develops in 1 in 1000 patients, usually within 3 months of therapy.
- Relapse in 50% within 2 years of stopping the drug.
- Nausea, vomiting and rash.

Important therapeutic features

- Clinical benefit is not apparent for 10-20 days (because half-life of already prepared thyroxin is 7 days).
- Clinically and biochemically patient becomes euthyroid at 3-4 weeks. Drug should be continued for 18-24 months in the following way:

Gradual dose titration

- Review after 4-6 weeks and reduce the dose of carbimazole depending on clinical state and T3, T4 and TSH level.
- Review after 2-3 months, if controlled, reduce the dose of carbimazole. Stop beta- blocker when patient becomes clinically and biochemically euthyroid.
- Gradually reduce the dose to 5 mg/day over 18-24 months.
- About 50% of patients will relapse within 2 years, long- term antithyroid therapy is then used or surgery or radioiodine therapy is considered.

Block and replace regimen
Full doses of carbimazole (40mg daily) are given to suppress the thyroid gland completely while replacing thyroid activity with 100 microgram of thyroxin daily once euthyroid state is achieved. This is continued for 18 months. This is claimed that with this regimen there is no under or over treatment.

Pregnancy and lactation
Smallest doe of carbimazole should be used (< 15 mg/day) and fetus should be monitored (fetal heart rate > 160/min strongly suggests fetal hyperthyroidism, carbimazole is given to mother). Over treatment can cause fetal goiter. Stop carbimazole 4 weeks before expected date of delivery to prevent possibility of fetal hypothyroidism. Breast-feeding while on usual doses of carbimazole appear to be safe, however propylthiouracil is preferred during pregnancy and lactation possibly causing less problems in the newborn. Side effects of propylthiouracil are arthritis, SLE, aplastic anemia, thrombocytopenia, acute hepatitis. Dosage: usual dose in non-pregnant is 300-600 mg in 4 divided doses while in pregnancy it should be below 200 mg/day.

CARBIMAZOLE

Dosage

- 0-3 weeks 40-60mg daily in divided doses
- 4-8 weeks 20-40 mg daily in divided doses
- Maintenance 5-20 mg daily

Duration of treatment
18-24 months

BETA- BLOCKERS

Propranolol (Inderal) 40-80 mg 8-hourly.

Mostly manifestations of hyperthyroidism are mediated via sympathetic system; therefore beta-blockers provide rapid symptomatic control. Beta-blockers also decrease peripheral conversion of T4 to T3.

SURGERY

Subtotal thyroidectomy

Indications

1. Recurrent hyperthyroidism after course of antithyroid drugs in patients of less than 40 years.
2. Initial treatment in males with large goiters and in those with severe hyperthyroidism.
3. Poor drug compliance

Precautions

1. Patient must be euthyroid before operation
2. Antithyroid drug is stopped 2 weeks before surgery and replaced by potassium iodide 600 mg TDS that reduces size & vascularity of the gland making surgery technically easier.

Complications

1. Postoperative bleeding, laryngeal nerve palsy
2. Hypothyroidism within one year
3. Recurrent hyperthyroidism

RADIOACTIVE IODINE

Indications

1. Patient more than 40 years
2. Recurrence following surgery

Mode of action

In acts either by destroying functioning thyroid cells or by inhibiting their ability to replace.

Complications

Hypothyroidism, approx in 40% in 1st year and in 80% after 15 years.

THYROID EYE DISEASE (Ophthalmic Grave's disease)

There are characteristic eye features in Grave's disease. It is suggested that exophthalmos is due to specific antibodies that cause retro-orbital inflammation and subsequent edema. It is not because of TSH or LATS.

Proptosis & limitation of eye movements are direct effects of the inflammation, while conjunctival edema, lid lag and corneal scarring are secondary to the proptosis and lack of eye cover.

EYE COMPLAINTS

History

- Difficulty in reading / distant vision
- Double vision
- Grittiness
- Protrusion

Physical signs

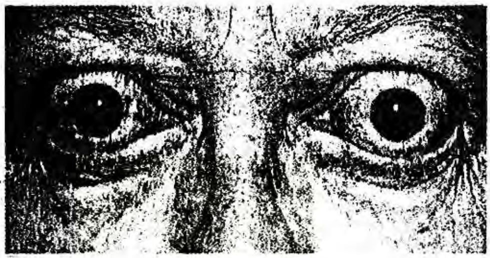
- Decreased acuity
- Limitation of eye movements
- Conjunctivitis / chmosis
- Lid lag / lid retraction
- Exophthalmos

Table . Comparison of the different treatments for the hyperthyroidism of Graves' disease

Management	Indications	Contraindications	Disadvantages/complications
Antithyroid drugs e.g. carbimazole	First episode in patients < 40 yrs	Hypersensitivity Breastfeeding (propylthiouracil suitable)	> 50% relapse rate usually within 2 years of stopping drug
Subtotal thyroidectomy	1. Recurrent hyperthyroidism after course of antithyroid drugs in patients < 40 yrs 2. Initial treatment in males with large goitres and in those with severe hyperthyroidism, i.e. total T_3 > 9.0 nmol/l 3. Poor drug compliance	Previous thyroid surgery Dependence upon voice, e.g. opera singer, lecturer[1]	Transient hypocalcaemia (10%) Hypoparathyroidism (1%) Recurrent laryngeal nerve palsy[1] (1%)
Radio-iodine	1. Patients > 40 yrs[2] 2. Recurrence following surgery irrespective of age 3. Other serious illness, e.g. multiple sclerosis irrespective of age	Pregnancy or planned pregnancy within 6 months of treatment	Hypothyroidism, approx. 40% in 1st year, 80% after 15 years Most likely treatment to result in exacerbation of exophthalmos

[1] It is not only vocal card palsy which alters the voice following thyroid surgery; the superior laryngeal nerves are frequently transected and result in minor changes in voice quality.

[2] In certain parts of the world, ^{131}I is used more liberally and prescribed for young women in the 20–40 age group.



The signs of thyroid eye disease, and its grading

Grade 0	No signs or symptoms
Grade 1	Only signs, no symptoms
Grade 2	Soft tissue involvment
Grade 3	Proptosis (measured with exophthalmometer)
Grade 4	Extraocular muscle involvement
Grade 5	Corneal involvement
Grade 6	Sight loss with optic nerve involvement

Management of opthalmopathy

The majority of patients require no treatment other than reassurance. Lid retraction will resolve when the patient becomes euthyroid and exopthalmos usually lessens gradually over a period of 2-3 years. For symptomatic ophthalmopathy following measures can be taken.

- *Steroid therapy:* prednisolone 60mg daily is given in exophthalmos if there is papilloedema, loss of visual acuity or visual field defect. Symptom relief with prednisolone is 64% in non- smokers and 14% in smokers.
- *Low dose radiation therapy* over 2 weeks to extraocular muscles is another treatment for exophthalmos.
- *Intravenous immune globulin* is as effective as prednisolone.
- *Orbital decompression surgery* is performed in severe cases to save the vision.

General eye protective measures

- *Methyl cellulose eye drops* will counter the gritty comfort of dry eyes.
- *Lateral tarsorrhaphy:* when there is corneal ulcer due to inability to close the lids.

THYROID CRISIS

Thyroid crisis is a medical emergency in which there is rapid deterioration of thyrotoxicosis with hyperpyrexia, severe tachycardia, vomiting, diarrhea, dehydration and extreme restlessness.

Precipitating factors: stress, infection, surgery in an unprepared patient or radioiodine therapy.

Management:

- Propranolol in full doses 0.5-2mg IV 4-hourly or 20-120mg orally 6- hourly.
- Carbimazole 25mg 6- hourly. Iodide is given 1 hour later as Lugol's solution or sodium iodide. Hydrocortisone 50mg 6 hourly.
- Aspirin should be avoided since it displaces T4 from thyroid- binding globulin.

TREATMENT OF TOXIC SOLITARY THYROID NODULES

- Definitive treatment is surgery or radioactive iodine. Propranolol is given to control symptoms.
- Carbimazole to make the patient euthyroid.

TREATMENT OF TOXIC MULTINODULAR GOITER

- As this disorder usually occurs in old age, radioactive iodine is preferred to surgery.
- Carbimazole to make the patient euthyroid and propranolol to control symptoms.

TREATMENT OF SUBACUTE THYROIDITIS

- Iopanoic acid 500mg orally daily to reduce serum T3 and is continued for 15-60 days.
- Propranolol to control symptoms.
- NSAIDs for pain.
- The condition subsides spontaneously within weeks to months.
- Carbimazole and radioactive iodine are ineffective.
- Watch for hypothyroidism that may follow the inflammatory episode.

TREATMENT OF HASHIMOTO'S THYROIDITIS

- It is more common in postpartum women.
- Propranolol to control symptoms.
- Watch for hypothyroidism.

TREATMENT OF CARDIOVASCULAR COMPLICATIONS

Sinus tachycardia
Non- selective beta – blocker (Propranolol).

Atrial fibrillation:

- Control hyperthyroidism.
- Electric cardioversion is usually ineffective to revert atrial fibrillation while the patient is thyrotoxic.
- Digoxin or beta blockers to control heart rate.
- Anticoagulation in some specific situations.

Heart failure

- Control of hyperthyroidism.
- Digoxin to rate control. Beta-blockers if rate not controlled with digoxin but give very cautiously because it may worsen the heart failure. Intravenous diuretic (frusemide) is required.

Angina

- Control of hyperthyroidism.
- Antianginal therapy

HYPERPARATHYROIDISM

ETIOLOGY

1. **Primary:** mostly due to parathyroid adenoma, less commonly due to hyperplasia or carcinoma.
2. **Secondary:** due to increased physiological demand for hormone in response to low serum calcium in chronic renal failure, malabsorption, rickets and osteomalacia.
3. **Tertiary**: due to development of parathyroid tumor against a background of prolonged secondary hyperparathyroidism.

Effects of hyperparathyroidism

- Hypercalcemia, hypercalciuria, renal stones, nephrocalcinosis.
- Chronic bone resorption produces demineralization that leads to pathologic fractures or cystic bone disease (osteitis fibrosa cystica).

CLINICAL FEATURES OF PRIMARY HYPERPARATHYROIDISM

Most common in woman over 50 years. If hyperparathyroidism presents before age 30, there is higher incidence of multiglandular disease such as multiple endocrine neoplasia (MEN).

1. **Onset:**
   Usually gradual with bone pain or swelling rarely sudden with fracture or renal colic.

2. **Features of hypercalcemia:**
   - Anorexia, nausea, constipation, muscular weakness, loss of weight, anemia, pruritus and hypertension.
   - Calcium may precipitate in cornea (band keratopathy) or soft tissue (calciphylaxis).

3. **Renal manifestations**
   - Polydipsia and polyuria due to hypercalcemia induced diabetes insipidus.
   - Hematuria and renal colic due to renal calculi
   - Chronic nephritis and hypertension.
   - Nephrocalcinosis and renal failure.

4. **Bony manifestations**
   - Decalcification and fibrosis – increased bone resorption by osteoclasts with fibrous replacement, clinically presenting with bone pain, tenderness, pathologic fracture and deformity.
   - Swelling of mandible due to cyst formation (rarely).
   - Falling of teeth
   - Loss of cortical bone and gain of trabecular bone.
   - Oseitis fibrosa cystica may also present as pathological fractures called "brown tumors".

Gastrointestinal features:

- Peptic ulceration is common.
- Pancreatitis may occur as a complication.

Neuromuscular disorders
Easy fatigability and paraesthesia.

CNS disorders

- Depression
- Psychosis

INVESTIGATION

1. **Serum calcium:** Raised (normal: 9-11 mg, hyperparathyroid: more than 11 mg)
2. **Serum parathyroid hormone (PTH):** Raised
3. **Alkaline phosphatase**: Raised if bone disease is present
3. **Serum phosphate**: Low (< 2.5 mg/dl).
4. Urine calcium excretion is high.
5. **Tc 99m sestamibi scan** (sensitivity 87%) to localize parathyroid adenoma that is usually very small and difficult to localize. Neck ultrasound (sensitivity 80%) or MRI may be used.
5. **X-rays:**
   - Cortical erosions most marked in phalanges especially radial aspects of fingers.
   - Salt- and- pepper appearance on lateral x-ray of skull
   - There may be cysts through out the skeleton.
   - Articular cartilage calcification (chondrocalcinosis) is sometimes found.

D/D of hypercalcemia

Malignancy (most common cause other than hyperparathyroidism) e.g. malignancy of breast, kidney, lung, thyroid, ovary and colon. Malignancy may be primary or metastatic.

CAUSES OF HYPERCALCEMIA
With normal or elevated PTH levels • Primary or tertiary hyperparathyroidism • Lithium-induced hyperparathyroidism • Familial hypocalciuric hypercalcaemia **With low (i..e suppressed) PTH levels** • Malignancy • e.g. lung, breast, renal ovarian, colonic and thyroid carcinoma • Multiple myeloma • Elevated 1,25(OH)2-vitamin D • e.g. Intoxication or sarcoidosis • Thyrotoxicosis • Paget's disease with immobilization • Milk-alkali syndrome • Thiazide diuretics

COMPLICATIONS

- Pathological fractures
- Urinary tract infection due to stone or obstruction – may lead to renal failure.
- Hypercalcemia may cause drowsiness, renal failure, and calcification is soft tissues throughout the body.
- Peptic ulcer and pancreatitis.
- Isulinoma, gastrinoma or pituitary tumors may be associated.
- Pseudogout.

TREATMENT

Surgical

Surgical removal of adenoma

<u>*Indications*</u>

Symptomatic patient

Symptomatic hyperparathyroidism, kidney stones or bone disease.

Asymptomatic patients

- Serum calcium 1mg/dl above the upper limit of normal with urine calcium excretion > 50mg/24 hours.
- Urine calcium excretion > 400 mg/24 hours.
- Cortical bone density > 2 SD below normal.
- Young patient under 50-60 years.
- Pregnancy
- Refractory to medical treatment.

Medical

- Hypercalcemia is treated with large fluid intake.
- <u>Bisphsphonates</u> are potent inhibitors of bone resorption and can temporarily treat hypercalcemia due due to any cause. Pamidronate, zoldetronate, alandronate may be used.

HYPERCALCEMIC CRISIS

It is medical emergency, especially elderly patient present with this condition.

Clinical featues: Dehydration, hypotension, abdominal pain, vomiting, fever and altered consciousness.

Treatment

- Fluid replacement 4-6 liters of normal saline within 24 hours
- Correction of electrolytes
- Lowering serum calcium with bisphosphonates
- Surgery as soon as possible after the patient has been rehydrated.

TREATMENT OF MALIGNANT HYPERCALCAEMIA

Rehydration with normal saline
To replace as much as 4-6 liter deficit
May need monitoring with central venous pressure in old age or renal impairment.

Bisphophonates, e.g. pamidronate 90mg i.v. over 4 hours

- Causes a fall in calcium which is maximal at 2-3 days and lasts a few weeks
- Unless the cause is removed, follow-up with an oral biphosphonate

Additional rapid therapy may be required in very ill patients

- Forced diuretics with saline and frusemide
- Glucocorticoids, e.g. prednisolone 40mg daily
- Calcitonin
- Haemodialysis

Treat the cause

HYPOPARATHYROIDISM

ETIOLOGY

1. Postoperative hypoparathyroidism: due to damage to the parathyroid glands during thyroid surgery (commonest cause).
2. Idiopathic hypoparathyroidism
3. Psudohypoprahypothyroidism: it is a congenital condition in which there is tissue resistance to the effects of parathyroid hormone. It presents with skeletal abnormalities, elevated levels of serum parathyroid hormone and normal serum calcium.

CAUSES OF HYPOCALCAEMIA

Incrased phosphate

- Chronic renal failure
- Phosphate therapy

Drugs

- Calcitonin
- Diphosphonates

Miscellaneous

- Acute pancreatitis
- Citrated blood in massive transfusion

Hypoparathyroidism

- Congenital deficiency (DiGeorge's syndrome)
- Idiopathic hypoparathyroidism (autoimmune)
- After neck operations
- Severe hypomagnesaemia

Resistance to PTH
Pseudohypoparathyroidism

Vitamin D

- Deficiency
- Resistance to vitamin D

CLINICAL FEATURES OF HYPOPARATHYROIDISM

- Features of tetany (in severe cases)
- Features of hypocalcemia e.g. paraethesia, numbness around the mouth, cramps, anxiety followed by convulsions, dystonia & psychosis
- Signs: trousseus sign & chvosteks sign

Management

- Parathyroid hormone preparations are unsatisfactory.
- Preparations of Vit. D (alfacalciodol) for persistent hypoparathyroidism are used. In acute phase calcium is given I/V.

TETANY

Increased excitability of peripheral nerves owing to either to a low serum calcium or to alkalosis in which the proportion of the serum calcium in the ionized form is decreased although the total calcium concentration remains unaltered.

CAUSES OF TETANY

Due to hypocalcaemia

- Malabsorption
- Osteomalacia
- Hypoparathyroidism]
- Acute pancreatitis
- Chronic renal failure

Due to alkalosis

- Repeated vomiting of gastric juice
- Excessive intake of oral alkalis
- Hyperventilation syndrome (a common medical emergency, mostly in girls due to some emotional factors presenting with tachypnea and carpopedal spasm).
- Primary hyperaldosteronism

CLINICAL FEATURES

In children: a characteristic triad of carpopedal spasm, stridor and convulsion occur. The hands in carpal spasm adopt a characteristic position, the metacarpophalangeal joints are flexed, the interphalangeal joints of fingers & thumb are extended and there is opposition of the thumb. Pedal spasm is less frequent & stridor is due to spasm of glottis.

In adults: tingling in the hands, feet and around the mouth. Less often thee is painful carpopedal spasm.

Latent tetany may be present when signs of tetany are lacking. This is best recognized by eliciting Trousseaus sign (inflation of the sphygmomanometer cuff on upper arm to more than the systolic blood pressure is followed by carpal spasm within 3 minutes). Chvosteks sign (gentle tapping over the facial nerve causes twitching of facial muscles).

MANAGEMENT

Control of tetany

Inj. Calcium gluconte initial 10ml I/V slowly than 10-40ml of 10% calcium gluconate in a litre of normal saline over 4-8 hours.

If tetany is not relieve by giving calcium gluconate then magnesium may be required.

Correction of alkalosis

I/V saline in persistent vomiting (which causes alkalosis) is most effective treatment

Ammonium chloride 2g orally, if excess alkali administration is the cause of alkalosis.

Rebreathing in paper bag in hyperventilation syndrome.

Chronic control of hypocalcemia

Vitamin D in the form of alfacalcidol which is converted in the liver into cacitriol. Dose is 0.5-3μg daily.

HYPERLIPIDEMIA

Lipids ciruculate in the body in the form of lipoproteins. On the basis of density, configuration and electrophoretic mobility, they are divided into the following types:

1. **Chylomicrons**
2. **Very low density lipoproteins (VLDL)** also called pre-betalipoproteins.
3. **Low density lipoproteins (VLDL)** also called bea-lipoproteins (high levels of these are predictive of coronary artery disease due to carrying cholesterol in large amounts which produces atheroma).
4. **High density lipoproteins (HDL).** High level of HDL protects from coronary heart disease because it carries small amount of cholesterol and it also reverses cholesterol synthesis.

ETIOLOGY OF HYPERLIPIDEMIA

Primary and secondary

Primary: (cause unknown)

Patient belonging to this hyperlipidemia can be divided into following types according to the genetic defect:

- Familial hypertriglyceridaemia
- Familial hypercholesterolemia
- Familial combined hyperlipidemia
- Lipoprotein lipase deficiency

Secondary (cause known)

Hypothyroidism, obstructive jaundice, nephrotic syndrome, anorexia nervosa, DM, CRF, alcohol.

PRIMARY HYPERLIPIDEMIA

Familial hypertriglyceridemia
History of pancreatitis or retinal vein thrombosis may be present.

Familial hypercholesterlemia
It is an autosomal dominant condition in which patients may develop excessive tissue deposits of cholesterol around the eye (xanthelsma), corneal arcus, or in tendons (xanthoma). The first evidence may be myocardial infarction occurring at early age (we have seen 14 years old boy with myocardial infarction – serum cholesterol was 2000 mg/dl). Approximately 50% of affected individuals will have a myocardial infarction by the age of 50.

Diagnosis can be made by clinical features, very high plasma cholesterol not responding to dietary modification and typical family history of early cardiovascular diseases.

Familial combined (mixed) hyperlipidemia
This is a common inherited condition characterized by the familial concurrence of hypercholesterolemia (raised LDL), hypertriglyceridema (raised VLDL) and sometimes both simultaneously in different members of the same family. There is increased risk of ischemic heart disease.

INVESTIGATIONS

1. Lipid profile is performed after at least 14-hour fasting. The patient follows his normal diet for the preceding 2 weeks and drugs that may affect lipid metabolism are withdrawn.
   - LDLs are major cholesterol-carrying lipoproteins in normal plasma. Its excess leads to coronary heart disease.
   - HDLs contain 20-50% of circulation cholesterol. It has protective role by lowering the LDL, thus preventing from coronary heart disease.
   - High HDL or triglyceride increase the risk of ischemic heart diseae whil the increased HDL provides protection
2. Investigations to detect other risk factors for coronary artery disease such as RBS for diabetes.

MANAGEMENT

General measures

- Dietary modification such as low-fat diet, reduce saturated fat, reduce calorie intake, high fiber diet. Effect of dietary modification should be pursued for 3-6 months, then start lipid lowering drugs in patients who have no ischemic heart disease or other risk factor.
- Avoidance of alcohol
- Avoidance of estrogen and thiazide
- Avoidance of smoking
- Moderate exercise, reduce weight
- Treatment of diabetes or hypertension when present.

Goals for treatment of LDL			
Risk category	LDL goal mg/dl	LDL at which initiate lifestyle chanes	LDL at which consider drug
Coronary heart disease	< 100	>100	>130
2 or >2 risk factors	<130	>130	>160
0-1 risk factor	< 160	> 160	> 190

Risk factors are DM, HTN, smoking

LIPID LOWERING DRUGS

1. **Pr Hypercholesterolemia:**

HMG CoA reductase inhibitors are first choice.

- Simvastatin (Tab. Zocor, Survive 10 & 20 mg). Usual dosage rang is 10-40 mg once daily at night.
- Atrovastatin (Lipitor 10, 20, 40 mg)---expensive but most effective as we see clinically.dosage: 10-80mg once at night.
- Lovastatin (Mevacor 20mg). Usual dosage is 20-80mg once daily at night.

Primary hypertriglyceridemia or combined hyperlipidema
Fibrates and nicotinic acid derivatives are first choice.

Fibrates

- Gemfibrozil (Lipoid 300mg). Usual dosage 600mg twice daily, max 1500 mg/d.

Drugs used in the management of hyperlipidaemia

Drug	Mechanism of action	Contraindications and adverse reaction	Expected lipid-lowering effect	Long-term safety
Fibric acid derivatives e.g. Gemfibrozil Bezafibrate Fenofibrate Ciprofibrate	Complex and not fully understood 1. Limit substrate availability for hepatic triglyceride synthesis 2. Modulate LDL/ligand interaction 3. Promote action of lipoprotein lipase 4. Stimulate reverse transport of cholesterol	*Contraindications* Severe hepatic or renal impairment, gallbladder disease, pregnancy *Adverse effects* Reversible myositis, nausea, predispose to gallstones, non-specific malaise, impotence	Reduction of LDL cholesterol by 10–15% and triglycerides by 25–35% HDL cholesterol concentrations increase by 0–15% (newer agents often have greater beneficial effect on HDL)	No knowledge of effect on developing foetus Avoid in women of childbearing age Medium-term safety appears good but there is little really long-term experience
Cholesterol binding resins e.g. Cholestyramine Colestipol	Anion exchange resins Bind bile acids in the gut, preventing enterohepatic circulation This promotes liver to convert cholesterol to bile acids Also stimulates formation of hepatic LDL receptors which take up more cholesterol from the circulation	*Adverse effects* Gastrointestinal adverse effects predominate: nausea, flatulence, abdominal bloating, alteration in bowel habit Palatability is a problem for some *Counselling* Other drugs bind to resins and should be taken 1 h before or 4 h afterwards	8–15% reduction in LDL Little or no effect on HDL cholesterol 5–15% rise in triglyceride concentration	Not systemically absorbed Safety profile is good and theoretically resins are of low risk in women of childbearing age Fat-soluble vitamin supplements may be required in children, pregnancy and breast feeding
HMG-CoA reductase inhibitors ('statins') e.g Simvastatin Pravastatin Atorvastatin Cerivastatin Fluvastatin Atorvastatin	Inhibit the rate-limiting step in cholesterol synthesis	*Contraindications* Active liver disease, pregnancy, lactation *Adverse effects* Derangement of liver function tests (recommended to measure liver function before and periodically during treatment) Myositis. Interferes with cyclosporin elimination and raises its blood concentration	30–40% reduction in LDL cholesterol Little effect on triglycerides or HDL cholesterol, except Atorvastatin modestly lowers triglycerides	Undetermined
Nicotinic acid and derivatives e.g. Nicotinic acid Acipimox	Unclear Probably inhibits lipid synthesis in the liver by reducing free fatty acid concentrations owing to an inhibitory effect on lipolysis in fat tissue	*Contraindication* Pregnancy, breast feeding *Adverse effects* Value limited by frequent side-effects: Headache, flushing, dizziness, nausea, malaise, itching, abnormal liver function Glucose intolerance, hyperuricaemia, activation of peptic ulcers, hyper-pigmentation may occur	Reduce LDL and triglycerides by 5–10% Modest HDL increase	Medium-term safety known but marred b the adverse effects listed
ω-3 marine triglycerides	Reduce hepatic VLDL secretion	Occasional nausea and belching	Reduces triglycerides in severe hypertri-glyceridaemia No favourable change in other lipids, and may aggravate hyper-cholesterolaemia in a	No long-term experience

Table Lipid-lowering drugs and their actions

Drug group	Principal actions
HMG CoA reductase inhibitors (e.g. simvastatin, pravastatin)	Inhibit cholesterol biosynthesis in the liver Activate hepatic LDL receptor Increase LDL catabolism Lower plasma and LDL cholesterol
Bile acid sequestrant resins (e.g. cholestyramine, colestipol)	Block intestinal reabsorption of bile acids Divert hepatic cholesterol into bile acid production Activate hepatic LDL receptors Lower plasma and LDL cholesterol
Fibrates (e.g. bezafibrate, fenofibrate)	Activate LPL Increase VLDL lipolysis Lower plasma triglyceride and raise HDL; reduce plasma LDL
Nicotinic acid and its derivatives	Inhibit lipolysis within adipocytes Reduce plasma free fatty acid levels Lower hepatic VLDL synthesis and secretion Lower triglyceride and increase HDL

ACTIONS OF INSULIN

Increases	Decreases
Carbohydrate metabolism • Glucose transport to muscle, adipose tissue. • Glucose phosphorylation • Glycogenesis • Glycolysis • Pyruvate dehydrogenase deficiency	• Gluconeogenesis • Glycogenolysis
Lipid metabolism • Triglyceride synthesis • Fatty acid synthesis • Lipoprotein lipase activity	• Lipolysis • Lipoprotein lipase activity • Ketogenesis • Fatty acid oxidation
Protein metabolism • Amino acid transport • Protein synthesis	Protein degradation.
Electrolytes Cellular potassium uptake	

DIABETES MELLITUS

Diabetes mellitus (DM) is a clinical syndrome characterized by chronic hyperglycemia and disturbances in carbohydrate, lipid and protein metabolism. The disease may result from defects in insulin secretion, insulin action (resistance) or both. Prevelance of diabetes mellitus is about 2-3%.

TYPES

PRIMARY DIABETES MELLITUS

- Insulin dependent diabetes mellitus (IDDM)
- Non-insulin dependent diabetes mellitus (NIDDM)

SECONDARY DIABETES MELLITUS

Pancreatic diseases
- Pancreatitis
- Hemochromatosis
- Cystic fibrosis
- Pancreactomy

Endocrine diseases
- Cushing's syndrome
- Acromegaly
- Thyrotoxicosis
- Pheochromocytoma
- Glucagonoma

Drug-induced
- Corticosteriod therapy
- Thiazide diuretics
- Phenytoin

Associated with genetic syndromes
- Freidreich's ataxia
- Myotonic dystrophy
- Down's syndrome
- Klinefelter's syndrome
- Turner's syndrome

Gestational diabetes
Diabetes of pregnancy

Differences between type 1 and 2 diabetes

Type 1 DM results from autoimmune destruction of the pancreatic islet beta cells with absolute loss of insulin secretion while the type 2 DM results from a combination of insulin resistance and insulin secretory defects.

Type 1 usually manifests in childhood with a peak age at 10-13 years, but it can present at any age. Type 1 can also occur in elderly and is described as latent autoimmune diabetes in adults. Type 2 diabetes usually manifests above 30 years, however type 2 diabetes is diagnosed in children as young as 6 years.

Maturity – Onset Diabetes of Young (MODY)

It is a rare variant of type 2 DM and is strongly inherited. The disease should be suspected in young people presenting with a typical family history and in whom other features of type 1 are lacking.

COMPARISON OF TYPE 1 AND 2 DM

Features	Type 1	Type 2
Precipitating factors	Unknown	Age, obesity, previous gestational diabetes
Endogenous insulin	Low or absent	Relative deficiency (the large amount required after meal is not released) Early hyperinsulinemia
Insulin resistance	Only with hyperglycemia	Mostly present
Prolonged fasting	Causes hyperglycemia, ketoacidoses	Glycemic level improves
Stress, withdrawal of insulin	Ketoacidosis	Non- ketotic hyperosmolar coma, occasionally ketoacidosis
C- peptide	Absent	Present

Table [illegible] Comparative clinical features of type 1 and type 2 diabetes

	Type 1	Type 2
Age at onset	< 40 years	> 50 years
Duration of symptoms	Weeks	Months to years
Body weight	Normal or low	Obese
Ketonuria	Yes	No
Rapid death without treatment with insulin	Yes	No
Autoantibodies	Yes	No
Diabetic complications at diagnosis	No	20%
Family history of diabetes	No	Yes
Other autoimmune disease	Yes	No

ETIOLOGY OF PRIMARY DIABETS MELLITUS

TYPE 1 (IDDM)

IDDM results from autoimmune disease process, following factors may be contributory:

1. **Genetic susceptibility:** is moderate; environmental factors required for expression, 30-35% concordance in monozygotic twins.
2. **Inheritance**: the child of an insulin dependent diabetic patient has an increased chance of developing IDDM. This risk is greater with diabetic farther than that of diabetic mother.
3. **HLA system:** 95% of IDDM patients carries HLA-DR3, HLD-DR4 or both genes.
4. **Viral infection**: antibodies to Coxsackie's virus B4 has been found in 20-30% patients, which reflects that viruses may be responsible for initiation or precipitation of the disease.
5. **Pancreatic pathology:** pancreas in pre-diabetic stage shows insulitis-infiltration with mononuclear cells Islet cell antibodies can be detected before the clinical evidence of IDDM.
6. **Immunological factors:** IDDM is a slow T-cell mediated autoimmune disease. Hyperglycemia accompanied by classical symptoms of diabetes occur only when 90% of beta cells have been destroyed.

PRE - TYPE 1 DIABETES MELLITUS

Islet autoantibodies appear in the circulation in the first few years of life in the first degree relatives of type 1 diabetes – demonstrating that the process culminating in diabetes is initiated very early and many years before diagnosis. This is called pre diabetes. This can predict development of diabetes in future.

TYPE 2 (NIDDM)

Exact cause unknown, following factors may be responsible:

1. **Genetics:**

Identical twins of a patient with NIDDM have an almost 100% chance of developing diabetes. About 25% of patients have a first-degree relative with NIDDM.

2. **Environmental factors:**

   Life-style: overeating especially when combine with obesity probably acts as a diabetogenic factor (increasing resistance to the action of insulin)

3. **Pancreatic pathology:**

   There are two pathological features in pancreas with NIDDM.

   - Reduction of insulin secretion cells.
   - Resistance to insulin action.
   - Delayed insulin secretion in response to oral glucose.

CLINICAL FEATURES

ONSET

- *Acute:* Patients with type 1 diabetes usually present with classic acute symptoms of hyperglycemia such as polyuria, thirst and weight loss and less frequently polyphagia, blurred vision and pruritus. Ketoacidosis may be the presenting feature in about 25% cases of type I.
- *Subacute:* In patients with type 2 diabetes, disease is often present for many years (on average 4-7 years) before diagnosis. Chronic hyperglycemia leads to polyuria, susceptibility to infection (balanitis, vaginitis) and slow wound healing.

MODES OF PRESENTATION

- With one or more common symptoms & signs
- On routine investigations
- Features of complications

PRESENTATION WITH COMMON SYMPTOMS AND SIGNS

Type 1 diabetes

Patients with type 1 diabetes usually present with:

1. *Polyuria* due to osmotic diuresis secondary to sustained hyperglycemia when blood glucose level exceeds the renal threshold.
2. *Thirst*: due to loss of fluid and electrolytes as a consequence of hyperosmolar state and osmotic diuresis.
3. *Weight loss:* due to depletion of glycogen (due to glycogenolysis) triglyceride stores (due to lipolysis) and due to reduced muscle mass as aminoacids are diverted to form glucose (gluconeogenesis). Therefore weight loss is a result of fluid depletion and accelerated breakdown of fat and muscle secondary to insulin deficiency. Usually there is no weight loss in type 2 diabetes.
4. *Blurring of vision:* it results from exposure of lens and retina to hyperosmolar fluids.
5. *Postural hypotension:* it results from lower plasma volume as a result of osmotic diuresis.
6. *Paraethesias:* due to temporary dysfunction of peripheral sensory nerves which becomes normal after glycemic control
7. *Ketoacidosis:* when absolute insulin deficiency is of acute onset, ketoacidosis develops. In about 25% of patients ketoacidosis is the first presentation.

CLINICAL FEATURES OF DIABETES AT PRESENTATION

Feature	Type 1	Type 2
Polyuria and thirst	++	+
Weakness	++	+
Polyphagia and weight loss	++	–
Recurrent blurred vision	+	++
Vulvovaginitis or pruritus	+	++
Peripheral neuropathy	+	++
Nocturnal enuresis	++	-

Type 2

Patients with type 2 may have history of increased urination and thirst but majority of them are asymptomatic initially. Type 2 patients usually present with lack of energy, delayed wound healing, visual blurring (due to glucose induced changes in refraction) and fungal infections such as pruritus vulvae or balanitis.

COMPLICATIONS AS THE PRESENTING FEATURE

Complication may be the first presenting feature:

1. *Infections*: skin infections, UTI, tuberculosis, pruritus vulvae or balanitis.
2. *Deterioration of vision* due to retinopathy
3. Paraesthesia, pain, muscle atrophy in the legs and impotence due to *neuropathy.*
4. *Diabetic foot:* Ulceration of feet due to combinations of neuropathy, infection & peripheral vascular disease.
5. *Myocardial infarction* due to atherosclerosis.

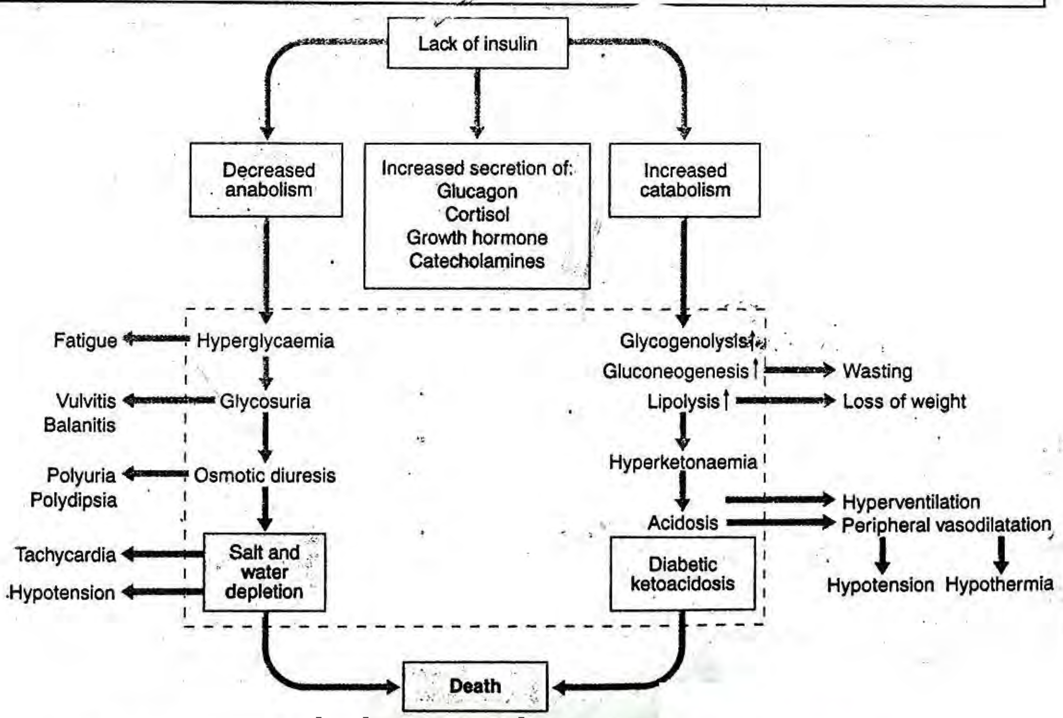
PRESENTATION ON ROUTINE INVESTIGATIONS

Diagnosis of diabetes is made when the investigations performed for other diseases.

CRITERIA FOR THE DIAGNOSIS OF DIABETES MELLITUS

	Normal	Impaired fasting glucose	Impaired glucose tolerance test	Diabetes mellitus
Fasting plasma glucose (mg/dl)	< 110	> 110 but < 126	-	> 126
2-hours after glucose load (mg/dl)	< 140	-	> 140 but < 200	> 200
Random (mg/dl)	-	-	-	> 200 with symptoms

Fasting: no solid or liquid food except water for at least 8 hours.
Random: any time of day, unrelated to meal.



Pathophysiological basis of the symptoms and signs of untreated or uncontrolled diabetes mellitus.

INVESTIGATIONS

Fasting blood sugar (FBS)
If fasting blood sugar is more than 126 mg/dl on more than one occasion, diabetes is confirmed

Random blood sugar (RBS)
If random blood sugar is more than 200 mg/dl, diabetes is labeled. However FBS is more reliable than RBS.

Glucose tolerance test (GTT)

1. After an overnight fat, 75g of glucose is taken in 250-300 ml of water.
2. Blood samples are taken in the fasting state and 2-hors after the glucose has been given.
   - Fasting blood sugar > 126 mg/dl is diagnostic of diabetes mellitus.
   - While impaired glucose tolerance is labeled when 2-hour glucose is more than 140 mg/dl but less than 200 mg/dl.
   - Diabetes is labeled when 2-hour blood glucose level is more than 200 mg/dl.
3. Glucose tolerance test is required for confirmation of diabetes when the fasting blood glucose is more than normal but less than in diabetic range (i.e. in between 110-126 mg/dl)

Glycosylated hemoglobin (hemoglobin A1c)

- Level of glycosylated hemoglobin reflects the state of glycemia over the preceding 8-12 weeks. Normal level is 4-6%. Adjustment of therapy is required if it is subnormal or more than 2% of upper limit of normal for that particular lab.
- Use of glycosylated hemoglobin for screening of diabetes is controversial, because its sensitivity is about 85% indicating that diabetes can not be excluded by a normal value, however elevated levels are quite specific (91%) in identifying the presence of diabetes.

Serum fructosamine
Serum fructosamine is formed by nonenzymatic glycosylation of serum proteins predominantly albumin. Serum fructosamine level reflects the state of glycemic control for the preceding 2 weeks. Normal values are 1.5-2.4 mmol/L when serum albumin level is normal (5g/dl).

Urinalysis to detect glucose in the urine.
Strips are sensitivity and can be used for detection of glucose in urine (glycosuria).

Other investigations

- Urine for proteinuria
- Complete blood count
- Urea, creatinine & electrolytes
- Fasting serum cholesterol and triglycerides

SYNDROME X
INSULIN RESISTANCE SYNDROME
METABOLIC SYNDROME
REAVEN'S SYNDROME

In obese patients with type 2 diabetes, there are cluster of features that are associated with atherosclerosis and macrovascular disease such as coronary, peripheral and cerebral artery disease, the basic defect is insulin resistance. Following are the features included in insulin resistance syndrome:

- Hyperglycemia
- Hyperinsulinema (compensatory)
- Dyslipidemia,
- Hypertension
- Hyperuricemia
- Central obesity
- Microalbuminuria
- Increased fibrinogen
- Increased plasminogen activator –1

All these features are due to insulin resistance (usually due to target tissue defect) This combination of features is called insulin resistance syndrome or metabolic syndrome or Reaven's syndrome or syndrome X.

GUIDELINE TO THERAPY FOR DIABETES

Type 1

- Diet therapy
- Insulin:

Type 2
Oral hypoglycemic agents

- Thin paitent – sulphonylureas
- Obese patient: biguanides

– Oral hypoglycemic agents are contraindicated in pregnancy
– The patient whose control is inadequate on tablets should start insulin without undue delay.
– Vascular complications including retinopathy can be reduced by regular low dose aspirin therapy.

TREATMENT

There are three methods available for the treatment of diabetes:

- Diet alone
- Diet & oral hypoglycemia drug
- Diet & insulin

DIET:

About 60% of diabetic patient can be treated adequately by diet alone. The diet should be balanced i.e. it should contain fat, protein and carbohydrates. Following steps should be taken in preparing any diet regimen.

Calories:

Decide the total daily requirement of calories, which depends upon the age, sex, weight, activity, occupation and financial resources. Diabetics who are obese should be treated with a strict low caloric diet.

An approximate calorie requirement of various groups is as following:

- Obese, middle aged or elderly patient with mild diabetes 1000-1600 kcal/day.
- Elderly diabetic but not overweight 1400-1800 kcal/day.
- Young, active diabetic 1800-3000 kcal/day.

Now estimate the proportion of calories derived from carbohydrates, protein and fat as follows:

- Protein – 10-15%
- Fat – 30-35%
- Carbohydrates 50-55%

Protein

The daily intake of protein should be 60-110 grams. An adequate amount of protein is required for the growth of the children.

Carbohydrate

The daily intake of carbohydrate should be 100-300 grams. All the carbohydrate should be in starch form. Readily absorbed carbohydrates, such as glucose & sucrose should be avoided, because they produce a sudden rise in the blood glucose level.

Salt

The daily intake of sodium should not be more than 6 grams / day.

Sweeteners

Non-nutritive sweetener such saccharine, aspartame (Candrel), sucramate make food palpable without energy gain.

Dietary fiber

Dietary fiber should be increased. It maybe soluble present in beans, peas, pulses, oats, fruits and vegetables—it can cause 10% reduction in fasting blood sugar and LDL cholesterol. Insoluble fiber present in wholemeal brad and cereals increases satiety and may beneficial for weight control.

Treatment of obese people with a diet low in refined and higher than in unrefined carbohydrate and restricted in total energy content result in increased insulin sensitivity which is associated with a rapid fall in the blood glucose concentration in obese diabetic.

Usually it is difficult to remember the amount of protein, carbohydrate and fat in different foods, therefore they should be written on all food products as written in the developed countries. Dietitians are also requested to help us in this field. Calorie chart is attached at the end of this section.

UNMEASURED DIABETIC DIET

Foods to be avoided altogether

Sucrose, glucose and foods high in sucrose / glucose.

Carbohydrate foods to be eaten in moderation

- Breads of all kinds, rolls, scones, biscuits, crispbreads; Breakfast cereals and porridge; potatoes, peas, baked beans;
- Alll fresh and dried fruit; pasta, custard, thick soups; diabetic foods, milk, meat, fish, eggs, cheese

Foods which can be eaten as designed

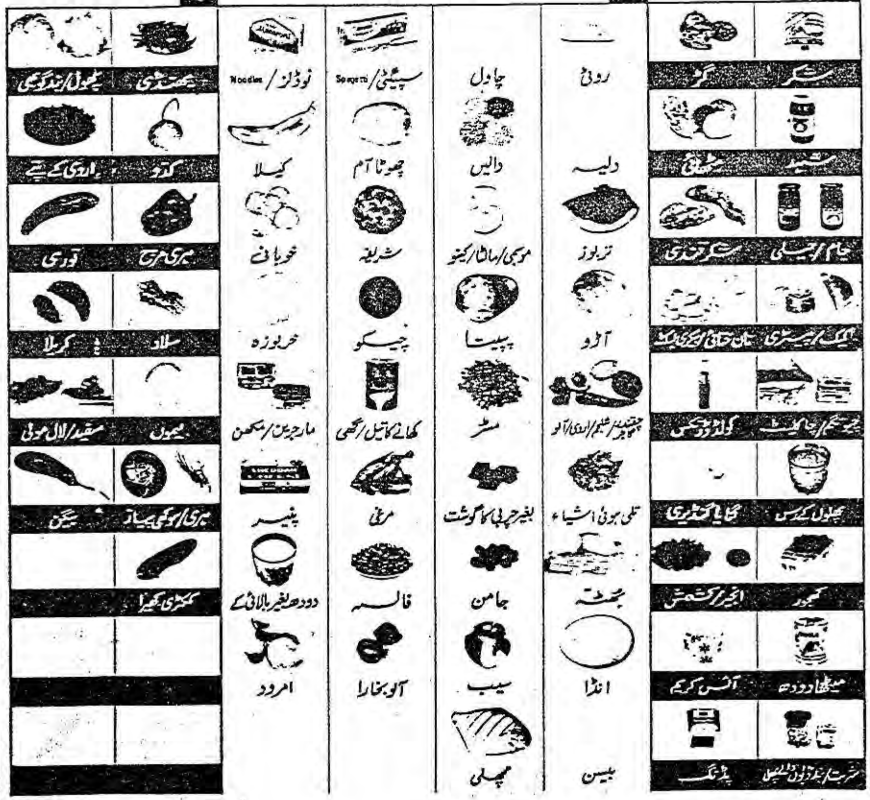
Green vegetables; clear soups, meat extracts, tomato or lemon juice; tea and coffee.

ذیابیطس کے مریضوں کے لئے ضروری ہدایات

غذا جو ذیابیطس کے مریض نہیں لے سکتے

غذا جو کم مقدار میں لے سکتے ہیں

غذا جو حسب ضرورت لے سکتے ہیں۔



دیگر مفید مشورے

1- دن میں کم از کم تین مرتبہ وقت پر کھانا کھائیے۔
2. اگر آپ دوا کے طور پر انسولین لے رہے ہیں تو شاید آپ کو کھانوں کے وقفہ میں ایک دو بار مختصر ناشتہ کی ضرورت پڑے۔
3. دن میں بکثرت پانی پیجئے (8-6 گلاس)۔ کھانے سے پہلے پانی کا استعمال بہتر رہے گا۔
4. تازہ پھل اور ترکاریاں کھائی جاسکتی ہیں، لیکن ان کے رس یا جوس سے پرہیز کیجئے۔
5. شکر، گڑ، شہد اور گلوکوز کے استعمال سے پرہیز کیجئے۔
6. اپنے دن بھر کے پروگرام میں جسمانی ورزش کو ضرور شامل کریں۔
7. اگر آپ کا وزن ضرورت سے زیادہ ہے تو آپ اپنے کھانے میں چربی، تیل، مکھن، مارجرین گھی، مقدار کم کر دیں۔
8. زیادہ چکنی اور تلی ہوئی چیزوں سے پرہیز کریں۔ خون میں چکنائی کی زیادتی کی صورت میں گوشت کے بجائے مچھلی اور مرغی کا استعمال مناسب رہے گا۔

آپ کی دن بھر کی غذا میں مندرجہ ذیل چیزیں شامل ہونی چاہئیں۔

1 دودھ اور دودھ سے بنی ہوئی اشیاء (بغیر چکنائی کے 2 کپ، پیالی)
2 گوشت / دالیں۔
تین چھٹانک گوشت (آدھ چھٹانک گوشت = ایک کپ دال کے)
3 روٹی اور دوسری اجناس۔ تین چپاتیاں (آدھی چپاتی، ایک ڈبل روٹی کے سلائس کے برابر)
4 سبزیاں۔ تین کپ (کٹی ہوئی) (ایک کپ کچی کٹی ہوئی سبزی = آدھا کپ پکی ہوئی سبزی کے برابر)
5 پھل ۔ 2 عدد
6 تیل۔ تین سے چار چائے کے چھوٹے چمچے

چند غذائی اشیاء کی کیلوریز

غذا	مقدار	کیلوریز
بھوسے والی روٹی	1 سلائس	80 کیلوریز
سفید ڈبل روٹی	1 سلائس	80 کیلوریز
چپاتی درمیانی	1 عدد	160 کیلوریز
چاول ابلے ہوئے	1/3 کپ	80 کیلوریز
دلیہ پکا ہوا	1/2 کپ	80 کیلوریز
دال ابلی ہوئی	1 کپ	80 کیلوریز
مچھلی / مرغی	1/2 چھٹانک	55 کیلوریز
گائے / بکرے کا گوشت	1/2 چھٹانک	75 کیلوریز
انڈا ابلا ہوا	1 درمیانہ	75 کیلوریز
کیلا	1 درمیانہ	120 کیلوریز
سیب / کینو	1 درمیانہ	60 کیلوریز
پپیتا / تربوز کٹا ہوا	1 کپ	60 کیلوریز
چکوترہ	1/2 درمیانہ	60 کیلوریز
آلو ابلا ہوا	1 درمیانہ	80 کیلوریز
مٹر ابلے ہوئے	1/2 کپ	80 کیلوریز
کھیرا کچا	1 کپ	14 کیلوریز
پھول گوبھی	1/2 کپ	16 کیلوریز
مولی کچی/کٹی ہوئی	1/2 کپ	20 کیلوریز
پیاز کچی/کٹی ہوئی	1/2 کپ	25 کیلوریز
دودھ بالائی والا	4 اونس	75 کیلوریز
دودھ بغیر بالائی	4 اونس	60 کیلوریز
آئسکریم	1 کپ	225 کیلوریز
کولڈ ڈرنک	12 اونس	140 کیلوریز
کھانے کا تیل	1 چائے کا چمچ	45 کیلوریز
گھی	1 چائے کا چمچ	45 کیلوریز
بادام	6 درمیانے	45 کیلوریز
مونگ پھلی	10 بڑے دانے	45 کیلوریز
ناریل پسا ہوا	2 بڑے چمچے	45 کیلوریز

ORAL HYPOGLYCEMIC DRUGS

These drugs are valuable in the treatment of patients with type 2 diabetes mellitus (NIDDM) who fail to respond to simple dietary restriction. Oral hypoglycemics are contraindicated in pregnancy. Sulphonylureas and biguanides are traditional drugs which are mainstay of treatment while there are certain new drugs available now.

- Sulphonylureas
- Biguanides
- Alpha glucosidase inhibitors (Acarbose)
- Non-sulphonylureas insulin stimulators (Repaglinide)

SULPHONYLUREAS

Sulphonylureas are used in non-obese patients of diabetes. These drugs act by:

- Improves early phase of insulin release that is refractory to glucose stimulation.
- Reducing peripheral resistance to insulin actions
- Reducing hepatic release of glucose.

Commonly used sulphonylureas

Glibenclamide (Daonil 5mg)

- Duration of action: 12-20 hours
- Recommended dosage: 2.5 20 mg/d
- Route of excrętion: renal
- Avoid: in renal failure, old patients because old patients are more prone to develop hypoglycemia, use short acting drugs in old age. Daonil can cause severe hypoglycemia.

Gliclazide (Diamicron 80mg)

- Duration of action: 10-12 hours
- Recommended dosage: 40-320 mg/d
- Largely metabolized by liver, therefore can be used in renal failure.
- Avoid: in hepatic impairment

Glipizide (Minidiab 5mg)

- Duration of action: 6-12 hours
- Recommended dosage: 2.5-40 mg/d 30 min before meal.
- Largely metabolized by liver, therefore can be used in renal failure.
- Preferable in elderly because of short duration of action.
- Avoid: in hepatic impairment .

Glimepride (Amaryl 1, 2, 3, 4 mg)

- Glimepride is a newer sulfonylurea that achieves blood glucose lowering with the lowest dose of any sulfonylurea.
- Dosage 1-8 mg.
- Long duration of action and therefore given once a day.
- It is completely metabolized in liver to relatively inactive metabolic products; and therefore may be used in renal impairment.

Sulphonylureas should be replaced by insulin during major surgery, severe illness & ketoacidosis. Steroids and thiazide diuretics reduce the clinical effects of the sulphonylureas.

Side effects

- Hypoglycemia
- GIT disturbances
- Obesity
- Water intoxication & hyponatremia

Contraindications: pregnancy

BIGUINIDES

These drugs act by decreasing glucose absorption from the gut. They are used in NIDDM when patients is overweight, and with the combination of sulphonylureas when sulphonylureas alone have proved inadequate to treat NIDDM. They are also called euglycemic drugs because they do not cause hypoglycemia if given to a non- diabetic person while sulfonylureas cause hypoglycemia in normal volunteers.

Mode of action

- Exact mechanism unknown.
- Reduces hepatic gluconeogenesis thus suppressing hepatic glucose output.
- Increases insulin sensitivity.
- Slowing down glucose absorption from GIT
- Increased uptake of glucose by skeletal muscles.

Metformin (Glucophage 500mg/1g)

The usual starting dose is 500mg 12-hourly with meal (to lessen the gastrointestinal side effects) increasing gradually to max 2 g daily in divided doses. There is no risk of hypoglycemia with this drug.

Side effects:

Gastrointestinal side effects such as anorexia, nausea, vomiting and diarrhea are common (20%).

Lactic acidosis: especially in renal failure and hypoxia such as in cardiac failure.

Contraindications

Metformin should not be given in the following conditions to avoid risk of lactic acidosis.

- Renal failure (serum creatinine >1.5 mg/dl).
- Hepatic insufficiency
- Alcoholism
- Cardiac failure
- Respiratory insufficiency such as in COPD.

ALPHA-GLUCOSIDASE INHIBITORS

These drugs inhibit glucose absorption from the intestine by inhibiting alpha-glucosidase enzymes situated on brush border of intestine and responsible for digestion of starch and sucrose. Therefore they delay the absorption of carbohydrate and lower the postprandial hyperglycemia.

Acarboes (Glucobay 50, 100 mg)

Acarbose is taken with each meal (usually with first bolus of food). It principally lowers postprandial blood glucose, modestly improves overall glycemic control and is now commonly prescribed to overweight patients with type 2 diabetes mellitus.

Side effects

Side effects are flatulence, abdominal bloating and diarrhea.

Miglitol

Miglitol is also an alpha- glucosidase inhibitor and is similar to acarbose. Dose 25 mg 3 times daily with meals.

NON-SULPHONYLUREAS INSULIN STIMULATIONS

These drugs stimulate insulin production at meal times (brief but rapid pulse of insulin).

Repaglinide (Novonorm 0.5mg, 1mg, 2mg)

Repaglinide is the meglitinide analogue. Starting dose is 0.5mg 15-20 min before each meal, maximum dose is 4mg before each meal (16mg/d).

- It is very rapidly absorbed from the intestine and metabolized in liver.
- Plasma half-life is less than 1 hour.
- It is preferable in elderly (due to short half-life) and in renal impairment (because it is metabolized in liver).

Side effects: hypoglycemia (but less than sulfonylureas), weight gain, transient elevation of liver enzymes, GI upset, rash and visual disturbances.

D- PHENYLALANINE DERIVATIVE

- Nateglinide is a D- Phenylalanine derivative and is similar to repaglanide in action; it causes brief and rapid insulin pulse and reduces postprandial rise in blood sugar if given before meals.
- It is rapidly absorbed from intestine, reaching plasma level within 1 hour.
- Metabolized in liver and plasma half-life is 1.5 hours.
- It can be given alone or in combination of metformin.

Nateglinide 120 mg 3- times daily with meals.
Side effects: weight gain, hypoglycemia.

THIAZOLIDINEDIONS

- These drugs sensitize the peripheral tissue to insulin.
- Rosiglitazone and Pioglitazone
- May be given alone or in combination of sulfonylureas or metformin. Pioglitazones is approved for use in combination with insulin.
- Dosage: pioglitazone (Piozer) 15-45 mg once a day, rosiglitazone 4-8 mg once daily.
- Side effects: weight gain, hepatotoxicity

INSULIN

Insulin is indicated in all patients with type 1 diabetes or patients with type 2 when hyperglycemia is not controlled with diet therapy or combination of diet and oral hypoglycemic agents.

TYPES

Ultrashort- acting- insulin

Absorption after subcutaneous injection of ultrashort acting insulin (insulin lispro) is very rapid and peak serum value is as early as 1 hour. Injection time before meal is 20 min (while short acting or regular insulin should be given 60 min before meal) so that there is no much waiting as long as 60 min after injection to begin the meal. Duration of insulin lispro is 3-4 hours.

Short-acting or regular or plain insulin

- Clear solutions
- Rapid onset (within 30 minutes after S/C injection)
- Short duration (6 hours)

Indications:

- New cases of diabetes with dehydration and/or ketoacidosis.
- In emergencies e.g. ketoacidosis or surgical operation.
- In all IDDM in combination of intermediate or long acting insulins.

Preparation

- Humulin - R (from human source): cost about Rs. 465.
- Actrapid HM (from human source): cost about Rs. 460.
- Actrapid beef (from bovine source): costs about Rs. 165.

Intermediate acting

- Cloudy solution
- Delayed onset (about 2 hours)
- Prolonged duration of action (18-24 hours) because insulin is pre-mixed with retarding agents e.g. protamine or zinc.

Indications:

In stable patient usually mixed with regular insulin.

Preparations:

NPH (neutral protamine Hagedorn) also called isophane available by the name Humilin N. Another preparation is Lente Humulin.

Mixtures of insulin

In majority of patients regular and NPH are given in combination. Regular is rapid acting and covers the meal while NPH works after 2 hours but has prolonged effect and covers the period upto the next injection.

- Mixtard 70/30 is a combination of regular (30%) and NPH (70%).
- Humulin 70/30

Long acting insulins

Humulin ultralente

It is given twice a day, it is often used to provide basal coverage while the short acting insulins are used to cover the glucose rise associated with meals.

Insulin glargine

- Insulin glargine is an insulin analogue in which the asparagines at position 21 of the A chain of the human insulin molecule is replaced by glycine and two arginines are added to the carboxyl terminal of the B chain.
- It is a clear insulin which when injected into the subcutaneous tissue, forms microprecipitates that slowly release the insulin into the circulation. It lasts for 24 – hours without any pronounced peaks and in given once a day to provide basal coverage.
- This insulin cannot be mixed because of its acidic pH.
- This insulin has advantage on NPH because given as a single injection at bedtime in type 1 patients; fasting hyperglycemia was better controlled and less chances of nocturnal hypoglycemia. In type 2 patients it is associated with a slightly higher progression of retinopathy when compared with NPH.

Site of injection:

Subcutaneous injection on abdomen, thigh, upper arm and buttocks. Repeated use of single site may cause fibrosis or lipodystrophy that can delay the absorption of insulin, therefore injection sites should be changes regularly.

Methods of insulin administration

- *Routes:* Subcutaneous, IM, IV.
- *Insulin syringe:* plastic disposable syringes are available in 1ml, and marked up to 100 units. These syringes may be reused until blunting. There is no need to clean needle with alcohol; just recapping is enough for sterility.

Insulin delivery systems:

- *Standard method of insulin administration with subcutaneous injections.* Prefilled insulin syringes of pen- size are also available (penfills) that eliminate the need to for carrying an insulin bottle and syringes (however expensive).
- *Infusion pumps:* continuous subcutaneous insulin infusion (CSII) pumps are very easy to use, small in size (about the size of pager).
- *Insulin by inhalation:* insulin inhalation before meal is also effective for glycemic control; however 300-400 units of insulin are required daily because only 10% of inhaled insulin is bioavailable. Only short acting insulin can be administered by this route. Studies are going on and it is not available in market now.

D- INSULIN – LIKE GROWTH FACTOR – 1 (IGF-1) THERAPY

In patients with severe insulin resistance who respond poorly to insulin, IGF-1 (a homologous to human proinsulin) is given as an IV bolus that produces hypoglycemia similar to insulin but through its own receptors. It is only advised for severe insulin resistance because it may promote tumor growth.

INSULIN RESISTANCE

Insulin resistance is defined as the requirement of 200 or more units of insulin per day to control hypoglycemia and prevent ketosis.

Insulin resistance may be at three sites:

- **Pre-receptor:** abnormal insulin or insulin antibodies.
- **Receptor:** decreased receptor number or diminished binding of insulin.
- **Post-receptor:** abnormal signal transduction, especially failure to activate receptor tyrosine kinase.

Anti-insulin antibodies appear within 60 days of initiation of insulin therapy in pre-receptor type resistance.

Treatment

High doses of glucocorticoids to suppress antibodies. Initially 80-100 mg prednisolone is required. Response occurs in 48-72 hours but may take longer. If no improvement after 3 weeks, it can be assumed that steroids will not be effective. Once insulin requirement begins to fall, reduce the dose of prednisolone until maintenance dose of 5-10 mg/day. Maintenance therapy may require for several months.

INSULIN REGIMENS

TREATMENT OF TYPE 1 (IDDM) WITH INSULIN

Insulin therapy is usually started on OPD basis; there is no need to admit the patient unless the first presentation is ketoacidosis.

Following methods may be used.

- Conventional split dose method
- Intensive insulin therapy

Conventional split dose method

In this method two injections per day are given, each injection is a combination of usually NPH and regular insulin.

Give two third (70%) of the calculated total insulin requirement in the morning before breakfast and one third (30%) in the evening before dinner. Each time there should be two third NPH and one third regular.

Morning: 2/3 of total dose (2/3 NPH + 1/3 regular)
Evening: 1/3 of total dose (2/3 NPH + 1/3 regular)

- Adults of normal weight may be started on 15-20 units a day. (In normal person average daily insulin production is about 25 units). Obese person may be started on 25-30 units a day.
- It is recommended that same quantity of insulin should be used for several days before changing, unless patient becomes hypoglycemic, whose dose should be reduced immediately. Generally changes should be no more than 5 to 10 units per step.

Example

Total calculated dose units / day.

- Morning: 20 units (14 units NPH 6 units regular)
- Evening: 10 units (6 units NPH and 4 units regular)

Intensive insulin therapy

This is used in those cases where above method cannot maintain near normalization of blood glucose without hypoglycemia, particularly at night and the multiple injections are used.

Three injections regimen

- Mixture of NPH and regular in the morning.
- Regular alone at dinner.
- NPH alone at bedtime.

Four-injection regimen

- Regular insulin before each meal (3 meals 3 injections)
- NPH or long acting (ultralente insulin) at bedtime.

Continuous subcutaneous insulin infusion

It can be given with a small battery driven insulin pump that delivers insulin subcutaneously into the abdominal wall throughout the day on basal rate.

TREATMENT OF TYPE 2 (NIDDM) WITH INSULIN

When sulphonylureas in combination with metformin fail, so the type 2 patients require insulin to control their hyperglycemia. Majority of diabetologists recommend that try to maximum doses of sulphonylureas and biguinides, then stop oral hypoglycemics and give only insulin, some diabetologist recommend daytime sulphonyluras and one injection of NPH at night.

Insulin alone in type 2 is used as following:

1. Single morning injection of NPH 25-30 units.
2. *Split dose method:* Already mixed NPH and regular 70/30 is used 20 units in the morning and 15 units before dinner (adjust the dose according to the sugar report).

Acceptable levels of glycemic control

- Fasting or before meals 90-130 mg/dl
- One hour after meal: < 180 mg/dl
- Two hour after meal < 150 mg/dl
- Hemoglobin A1c (HA1c) not more than 2% of upper normal limit.

COMPLICATIONS OF INSULIN THERAPY

- At the site of injection: injection abscess, lipodystrophy (lipoatrophy or lipohypertrophy)
- Insulin resistance – mostly due to obesity. Formation of IgG antibodies against insulin that neutralize the action of insulin.
- Weight gain
- Hypoglycemia is the most common complication.

CLINICAL TRIALS IN TYPE 1 DIABETES

Diabetes trials is a common viva question now, try to remember the outcomes of these trials.

Diabetes prevention trial – 1 (DPT-1)

Daily low dose insulin injections in first – degree relatives of type -1 diabetics who were selected as being at risk for development of type –1 diabetes because of detectable islet cell antibodies. Trial was stopped because it failed to show benefit of prophylactic insulin therapy.

The diabetes control and complication trial (DCCT)

This trial was done on type 1 diabetics. It showed that intensive insulin therapy with multiple insulin injections markedly reduces the risk of diabetic complications; however with risk of serious hypoglycemia. Reinterpretation of DCCT trial suggests moderate glycemic control (HbA1c no higher than 2% above the normal limits).

CLINICAL TRIALS IN TYPE 2 DIABETES

The diabetes prevention program (DPP)

This trial was performed in overwight persons and showed that low – fat- diet and 150 min brisk walk/week reduces the risk of progression to type 2 diabetes by 58% as compared with a matched control group.

The United Kingdom prospective diabetes study (UKPDS)

This study shows that intensive therapy with either sulfonyluria, metformin, combination of two or insulin therapy achieving HA1c level of 7% decreases the risk of microvascular complications (retinopathy and nephropathy) as compared with diet therapy. However there was no cardiovascular benefit. Strict hypertension control in diabetes reduces the risk of complications.

MANAGEMENT OF EARLY MORNING HYPERGLYCEMIA IN TYPE 1 DIABETES.

(A very common viva question)

One of the more difficult problem in the management of type 1 diabetes is the determining the proper adjustment of insulin dose when the fasting blood sugar is high. This high fasting sugar may be due to several mechanisms as following:

Somogyi effect:

- Patient with type 1 diabetes may develop nocturnal hypoglycemia (due to high dose of night NPH insulin) which may inturn stimulate a surge of counter- regulatory hormones (Somogyi effect) to produce high blood glucose levels by 7 AM.
- Check blood sugar at 3 AM (low) and 7 AM (high).
- Reducing (not increasing) inappropriate doses of night NPH improves the morning hyperglycemia.

Dawn phenomenon

- The dawn phenomenon occurs in about 75% of type 1 patients, also occurs in type 2 and in normal persons. It is characterizewd by reduced tissue sensitivity to insulin developing between 5-8 AM causing fasting hyperglycemia.
- It may be due to spikes of growth hormone released at the onset of sleep.
- Blood sugar at 3-4 AM (not low) and at 7AM (high).
- Management: divide the dose of night NPH into pre- dinner and at bedtime.

Wanning of circulating insulin

- The most common cause of fasting hyperglycemia is the waning of circulating insulin level.
- Management is to increase night NPH or change it from dinnertime to bedtime to achieve sustained response the whole night.

Whole pancreas and pancreatic islet transplantation

Whole pancreas and pancreatic islet transplantation as a treatment of diabetes are in clinical trials. The main disadvantage is the need for powerful immunosuppressive therapy.

ASSESSMENT OF DIABETIC CONTROL

- Blood glucose
- Urinary glucose
- Glycosylated hemoglobin (HBA1) conc.

Glycoslated hemoglobin (HbA1c)

When hemoglobin from a normal adult is passed through a chromatographic column it separates into:

- The major components; collectively known as hemoglobin A (HbA) comprising 92-94% of total hemoglobin.
- The minor components; collectively known as hemoglobin A1 (HbA1c) comprising 4-6% of total hemoglobin.

HbA1c is identical to HbA except for the addition of a glucose group to the terminal amino acid of beta chain of hemoglobin molecule. Therefore rate of synthesis of HBA1c depends upon exposure to the red cells to the glucose. Since the glucose linkage to hemoglobin is relatively stable, HbA1c accumulates throughout the life span of the erythrocyte and its concentration reflects the mean blood glucose concentration over the previous 8-12 weeks.

- Measurement of HbA1c should be made in patients with either type of diabetes mellitus at 3-4 months interval to estimate blood glucose control over about three months period.

EDUCTION OF PATIENT

Patient should be educated about the following important aspects of management, prevention and recognition of complications:

- Patient should be taught how to check blood sugar with a glucometer
- Detection of ketone bodies on urine analysis on strips.
- How to measure the accurate dose of insulin.
- Recognition of symptoms of hypoglycemia and management.

- Ask the patient to carry a card stating his name, diagnosis, doses of insulin and telephone number of family doctor.
- Patient should be taught how to maintain hygiene. *Keep feet as clean as face.*

CHECKLIST FOR FOLLOW-UP VISITS OF PATIENTS WITH DIABETES MELLITUS

Body weight

Urinalysis
Urinalasis of fasting specimen for glucose, ketones, albumin (both macro and microalbuminuria)

Glycaemic control
- GHb (HbA1c)
- Inspection of home blood glucose monitoring record

Hypoglycaemic episodes
- Number of serious (requiring assistance in treatment) and mild episodes
- Time when 'hypos' experienced

Blood pressure (supine and erect)

Visual acuity
Ophthalmoscopy (with pupils dilated)

Lower limbs
- Peripheral pulses
- Tendon reflexes
- Perception of vibration sensation
- Feet: ulceration, callous skin indicating pressure area, nails, need for chiropody

EXAMINATION OF DIABETIC PATIENT

(One of the commonest physical examination performed in long and short cases)

General appearance
- Weight: obesity
- Facial appearance: Cushinoid face
- State of hydration

Lower limbs (start examination from legs)

Inspection
- Necrobiosis lipodica: yellow scared area due to atrophy of subcutaneous collagen.
- Skin atrophy due to insulin use
- Ulceration
- Infection
- Hair loss, skin atrophy (due to ischemia)
- Look at thigh for injection sites, quadriceps wasting (femoral nerve mononuritis).

Palpation
- Temperature: cold due to ischemia
- Peripheral pulses (femoral, popliteal, posterior tibial, dorsalis pedis)
- Edema (due to nephropathy).

Neurological assessment
- Sensations including those of dorsal column.
- Reflexes: diminished due to neuropathy.
- Proximal muscle: for wasting.
- Joints: for Charcot's joints (loss of proprioception)

Upper limbs
- Nails: for candidiasis
- Feel upper arm injection sites
- Blood pressure in supine and standing to detect autonomic neuroapathy.
- Pulse (resting tachycardia due to autonomic neuropathy)

Eyes
- Visual acuity (because cataract is common)
- Examine third, fourth and sixty cranial nerves (cranial nerve palsy may be present).
- Fundoscopy for retinopathy (especially neovascularizaiton).
- Periorbital and perinasal swelling with gangrene due to rhinocerebral mucormycosis (fungal infection)

Head and neck
- Look mouth for candidiasis
- Ear for malignant otitis externa due to pseudomonas.
- Feel for carotid bruit.

Abdomen
- Hepatomegaly: due to fatty liver.

COMPLICATIONS OF DIABETES	
Acute complications	
• Hypoglycemia • Diabetes ketoacidosis (DKA) • Non-ketotic hyperosmolar coma	
Chronic complications	**Presentations**
Microvascular	
1. Retinopathy, cataract	1. Impaired vision
2. Nephropathy	2. Renal failure
3. Peripheral neuropathy	3. Sensory loss, motor weakness.
4. Autonomic neuropathy	4. Postural hypotension, impotence, gastropathy.
5. Foot disease	5. Ulceration, infection.
Macrovascular	
1. Coronary artery disease	1. Angina, MI
2. Cerebral ischemia	2. TIA. Stroke
3. Peripheral vascular disease	3. Claudication

HYPOGLYCEMIA

CAUSES:

- Imbalance between injected insulin and patients normal diet, activity & basal insulin requirement.
- Irregular eating habits, unusual exertion and alcohol excess may precipitate episodes.
- Impaired ability to counter – regulate glucose levels after hypoglycemia in diabetic patient is also responsible for episode. Glucagon response is lost. Adrenaline response may also fail in patients with a long duration of diabetes.

Cause of hypoglycaemia related to diabetes

- Missed, delayed or inadequate meal
- Unexpected or unusual exercise
- Alcohol
- Poorly designed insulin regimen, particularly that predisposing to nocturnal hypoglycemia.
- Deficient glucose counter-regulation/impaired awareness of hypoglycemia.
- Gastroparesis due to autonomic neuropathy
- Unrecognized other endocrine disorder e.g. Addison's disease
- Malabsorption
- Factitious (deliberately induced)
- Errors in oral hypoglycaemic agent or insulin
- Errors in oral hypoglycaemic agent or insulin dose/schedule/administration.

Clinical features

Symptoms of hypoglycemia begin at plasma glucose 60mg/dl; brain impairment develops at approximately 50 mg/dl. Brain damage after prolonged severe hypoglycemia is not reversible.

Features of hypoglycemia are:

- Pallor, tachycardia, palpitation, sweating, nausea and tumor (due to stimulation of sympathetic system as a counter regulatory mechanism which increases blood glucose by increasing glycogenolysis).
- Hunger due to parasympathetic stimulation
- Mental confusion, aggression or convulsion.
- Some patients with long duration of diabetes have not such symptoms and go into severe hypoglycemia. Patients become pale & drowsy. Mental confusion or convulation & rapidly occurring hypoglycemic coma (due to decreased supply of glucose to the brain).

Whipple's triad

It is a group of features related to hypoglycemia due to any cause and consists of:

1. History of hypoglycemic symptoms.
2. Fasting blood glucose of 40mg/dl or less.
3. Immediate recovery after administration of glucose.

SYMPTOMS OF HYPOGLYCEMIA	
Autonomic • Sweating· • Trembling· • Pounding heart· • Hunger· • Anxiety	**Neurologic** • Confusion· • Drowsiness· • Speech difficulty· • Inability to concentrate· • Incoordination
Non-specific • Nausea· • Tiredness • Headache	

Treatment

- Patient conscious: oral glucose drink
- Patient unconscious: 50 ml of 50% dextrose water I/V or Inj glucagon 1mg I/M
- Precaution: patient should carry some tablets of glucose for use in emergency.
- If severe hypoglycemia causes unconsciousness or stupor, the treatment is 50ml of 50% glucose solution by rapid IV infusion. If intravenous therapy is not available, 1mg of glucagons injection IM will usually restore the patient to consciousness within 15 min. If the patient is stuprous and glucagons is not available, small amount of honey or syrup can be inserted within the buccal pouch. Rectal administration of honey or syrup (30ml/500ml of warm water) has been effective.
- NOTE: Injection glucagon is not effective for hypoglycemia caused by oral hypoglycemic drugs, it is effective for insulin induced hypoglycemia:
- Patients with hypoglycemia caused by oral hypoglycemic agent or long acting insulin should be admitted and observed because hypoglycemia may be recurrent due to the prolonged duration of these drugs.

DIFFERENTIAL DIAGNOSIS OF HYPOGLYCEMIA

1. Starvation
2. Insulinomas – pancreatic inlet cell tumors that secrete excessive insulin.
3. Along with other tumors e.g. sarcomas
4. Fulminant hepatic failure
5. Drug induced:
    - Sulphonylureas taken by non-diabetic
    - Aspirin ingestion by children
    - Propranolol in the presence of starvation of strenuous exercise
6. Alcohol induced
7. Endocrine causes
    - Hypopituitarism
    - Isolated ACTH deficiency
    - Addison's diseases

HYPOGLYCEMIA DUE TO PANCREATIC B CELL TUMORS (INSULINOMAS).

Fasting hypoglycemia may be due to an adenoma of the islets of Langerhans, 90% are single and benign, rarely multiple and malignant.

Diagnosis

Elevated serum insulin in the presence of hypoglycemia (insulin level 6μU/ml or more when blood glucose is < 40mg/dl). An elevated proinsulin level in the presence of hypoglycemia is characteristic og most B cell adenomas and does not occur in factitious hyperinsulininsm.

Prolonged fasting under hospital supervision until hypoglycemia is documented is the most diagnostic tool. In a normal person blood glucose does not fall below 55-60mg/dl during a 3- day fast while in insulinoma blood sugar level can drop to 35mg/dl, patient becomes symptomatic earlier and serum insulin level is high.

Proinsulin: proinsulin level in normal person is < 20% of total insulin while in insulinoma it becomes 30-90% of insulin.

Stimulation test: intravenous glucagons stimulates insulin secretion and causes very high serum insulin level. This test is performed in borderline fasting hyperinsulinism.

Preoperative localization of tumor
Insulinomas are very small and usually not detected on CT or MRI. They are diagnosed on intraoperative ultrasound and palpation by an experienced surgeon.

Treatment
1. Surgery
2. Medical treatment
    - Carbohydrate feeding every 2-3 hours (hypoglycemia not responding to glucose).
    - Glucagon injection should be available for emergency.
    - Diazoxide or calcium channel blocker (verapamil) or octreotide or streptozocin may be used to inhibit insulin release from insulinoma.

DIABETIC KETOACIDOSIS

Diabetic ketoacidosis is a medical emergency with mortality rate about 5%. It may be the initial manifestation of type 1 diabetes or may result from increased insulin requirement in type 1 diabetes patients during the course of stress such as infection, trauma, surgery or myocardial infarction. Type 2 diabetics may develop ketoacidosis under severe stress such as infection or trauma.

PRECIPITATING FACTORS

1. Acute infection: bacterial or viral
2. Omission or drastically reduction the dose of insulin
3. New onset of type 1 diabetes (about 25% patients of type 1 are first time diagnosed when they present with ketoacidosis).

DIAGNOSIS

1. Hyperglycemia (usually: >250 mg/dl)

The magnitude of hyperglycemia does not correlate with the severity of metabolic acidosis: moderate elevation of blood glucose may be associated with life-threatening ketoacidosis. In some cases hyperglycemia predominates with minimal acidosis. There is ++++ glycosuria.

2. Metabolic acidosis

- Blood pH < 7.3
- Serum bicarbonate < 15 meq/L

3. Hyperketonemia and ketonuria

Urinary ketones strongly positive ++++

PATHOPHYSIOLOGY

Hyperglycemia

Without effective circulating insulin levels, blood glucose concentrations rise, eventually producing an osmotic diuresis with the loss of fluid and electrolytes. This results in dehydration (usually 4-6 liter), depletion of total body potassium (about 300 mmol and lesser degree of sodium (about 500 mmol), chloride, phosphate and magnesium. These electrolytes are lost due to osmotic diuresis.

Metabolic acidosis

Lack of insulin absolute or relative, causes increased release of fatty acids from adipose tissue and increased ketone bodies production from these acids. Ketone bodies are produced more rapidly than can be metabolized and therefore accumulate. Accumulation of acid in the form of ketone bodies causes fall in blood pH with characteristic hyperventilation, negative inotrophic effect on heart and peripheral vasodilatation with consequent hypotension. Therefore due to metabolic acidosis patient develops hypotension and hyperventilation. Hydrogen ions also displace intracellular potassium which is then lost in the urine.

REVIEW TABLE PATHOPHYSIOLOGY OF KETOACIDOSIS

Hyperglycemia leads to hyperosmotic diuresis causing

- Dehydration
- Hypovolemia
- Na+, K+ and other electrolyte depletion

Acid accumulation

- Hyperventilation
- Negative inotropic effect on the heart
- Peripheral vasodilatation (hypotension)
- Potassium depletion

CLINICAL FEATURES

Features of dehydration and acidosis

Symptoms

- Intense thirst
- Poyuria
- Nausea, vomiting
- Abdominal pain more common in children

Signs

- Dry tongue, inelastic skin, sunken eyes
- Kussmaul's respiration (rapid and deep breathing)
- Abdominal tenderness (may be)
- Hypotension
- Rapid weak pulse
- Hypothermia
- Fruity breath odor of acetone

- Level of consciousness is variable, patient with severe ketoacidosis may be conscious and alert, drowsiness is usual but coma is uncommon. Level of consciousness depends on serum osmolality, not on level of acidosis. When serum osmolality exceeds 320-330 mosm/L, CNS depression or coma develops (normal value is 280-300 mosm/L)

Formulate for calculation of serum osmolality is:

$$\text{Serum osmolality} = 2\,[\text{Na}] + \text{K} + \frac{\text{glucose mg/dl}}{18}$$

INVESTIGATIONS

1. Blood glucose and electrolytes hourly for 3 hours and then every 2-4 hour thereafter.
2. Elevated anion gap: it is the difference between cations and anions and is measured by the following formula:

Anion gap = [sodium + potassium] – [chloride + bicarb]

Normal anion gap is 12 plus minus 2 mmol/lit. The normal anion gap is because of anionic plasma protein (albumin) while the elevated anion gap signifies overproduction of an organic acid.

3. **Urinary ketones:** Urine is strongly positive for ketone bodies (check urinary ketones every 4 hourly). Ketonuria can persist after correction of acidosis.
4. **ABGs** show low pH, low bicarb. ABG is usually performed once and only repeated if serum bicarbonate is not elevated 4-6 hours of insulin therapy.
5. **Blood CP:-** high WBC counts (leukocytosis). TLC may be as high as 25000 with a left shift with or without infection.
6. **X-ray chest:** to look for infection.
7. **ECG:** to exclude myocardial infarction and to monitor K+ level.
8. **Urea and creatinine:** to measure renal status.
9. **Plasma osmolality**: level exceeding 320-330 mosm/L can lead to CNS depression and coma.

MONITORING IN KETOACIDOSIS

- Fingerstick blood glucose and electrolytes hourly for 3 hours then 2-4 hourly thereafter.
- BP, pulse, temperature and respiration hourly.
- Urine output
- Urinary ketones – 4 hourly
- ECG, ABGs, plasma osmoality

MANAGEMENT

Diabetic ketoacidosis is a medical emergency and should be treated in hospital. The principles of treatment are:

1. Fluid replacement
2. Regular or plain insulin by I/V or I/M
3. Potassium (K+) replacement
4. Antibiotics if infections are present.

Fluid replacement

Average fluid deficit is about 6 liters.

- 3 liters from extracellular compartment, replaced by normal saline (.9% NaCl)
- 3 liters from Intracellular compartment, replaced by dextrose water (0.5% glucose).
- However 6 liters fluid is not required by every patients, it depends on degree of dehydration. Therefore check JVP, basal crepts and urine output during fluid replacement, fluid overloading causing pulmonary edema is not an uncommon complication especially if management is performed by junior doctors.

Scheme

First we correct extracellular and then intracellular deficit.

Normal saline 0.9% NaCl

- 1 liter in ½ hour, then
- 1 liter in 1 hour, then
- 500 ml per hour

Bicarbonate

If there is severe acidosis (pH < 7.0) 1-2 ampoules of sodium bicarbonate (44 mEq per 50 ml ampoule) may be given over 30 min in hypotonic saline (0.45% saline) in place of same volume of normal saline. The combined administration of insulin and bicarbonate increases the risk of hypokalemia so that the potassium should be given along with bicarbonate.

Dextrose water (D5W)
When the blood glucose level falls to 250 mg/dl, normal saline is replaced by 5% dextrose water with 0.45% saline (D5W + ½ NS) with reduced dose of insulin (1-4 units hourly) until the ketonuria has disappeared and the water deficit has been made good. Maintain blood glucose between 200 and 300 mg/dl.

- Early and rapid rehydration is essential; otherwise the administered insulin will not reach the poorly perfused tissues.

Insulin

- First give loading dose of regular insulin 0.1 unit/kg IV bolus then 0.1 units/kg/hr in a continuous infusion.
- If infusion is not possible then 10 units IM stat then 4-6 units in IM hourly.
- Blood glucose level should decrease by 100 mg/dl/hour.
- If blood glucose levels do not fall at least 10% in the first hour, a repeat loading dose is recommended. Double the infusion rate every 2-hours until blood glucose level begins to fall by at least 10%.
- When the blood glucose conc. has fallen to 250 mg/dl, the dose of insulin should be reduced to 1-4 units hourly.
- The subcutaneous route is avoided because subcutaneous blood flow is reduced in shocked patients.
- Very rapid fall in blood sugar should be avoided because it can lead to cerebral edema.

Potassium replacement

- All patients in diabetic ketoacidosis are potassium depleted and nearly all will require I/V potassium to prevent dangerous hypokalemia. Therefore add 20 mmol of KCl to each litre except in first litre because plasma K+ level is often high at presentation due to reduced entrance of K+ in the cell in the deficiency of insulin.
- Potassium should be replaced even the report is awaited if ECG shows no hyperkalemia and patient is passing urine. Otherwise wait for the report of electrolytes because patient might have renal failure in which potassium would be already raised.
- If ECG shows flat T wave or formation of U wave that indicate hypokalemia, potassium management with fluid and insulin will cause further hypokalemia. Fluid replacement dilutes plasma causing life-threatening hypokalemia. Insulin also shifts potassium inside the cell that can also lead to hypokalemia.

Antibiotics
These are given after detection of infection and according to the type of infection. Meanwhile broad-spectrum antibiotics should be given.

Special measures

- Bladder catheter if no urine is passed after two hours.
- Nasogastric tube to keep stomach empty in unconscious or drowsy patient because dilated stomach is one of the complications of ketoacidosis and to prevent aspiration in the drowsy patient.
- CVP line in shocked patient so the fluid given can be adjusted accurately.
- For DVT prophylaxis subcutaneous heparin in comatose, elderly or obese patient because thromboembolism is one of the complication of ketoacidosis.

Subsequent monitoring
After initial rehydration and electrolytes and insulin administration, subsequent management is as follows:

- Monitor glucose hourly for 8 hours
- Monitor electrolyte 2 hourly for 8 hours
- Adjust potassium replacement according to the results

Monitor the ketoacidic patient for 24 hours. Once ketoacidosis has been overcome, feeding by mouth can be started with frequent small fluid feeds each containing 25g carbohydrate.

Subsequent management
Once the patient is able to drink fluids and the ketoacidosis has resolved (indicated by decreased anion gap, and rise in serum bicarbonate) subcutaneous injection of insulin may be started, discontinue IV infusion 30min after the subcutaneous dose.

COMPLICATIONS OF KETOACIDOSIS

Hypotension

Hypotension can lead to renal failure. Plasma expanders (such as Hemaccel) or whole blood may be given if systolic blood pressure is below 80 mmHg and not responding to normal saline.

Cerebral edema

It may be caused by rapid reduction of blood glucose or use of hypotonic fluids. Mortality is high; treat with *mannitol and oxygen.*

Acute respiratory distress syndrome (ARDS)

It manifests as hypoxemia on ABG or pulse oximetry and as pulmonary infiltrates on chest x-ray.

Thromboembolism

T prevent DVT and other forms of thromboembolism give heparin in unconscious, elderly or obese patient.

Disseminated intravascular coagualtion (DIC)

It is rare.

Hypothermia

Severe hypothermia may occur in ketoacidosis.

Complicaitons of therapy

Hypoglycemia, hypokalemia, pulmonary edema.

HYPEROSMOLAR NON-KETOTIC COMA

This condition, in which severe hyperglycemia develops without significant ketosis, is the metabolic emergency characteristic of uncontrolled type 2 diabetes. Patients present in middle or later life, often with mild or previously undiagnosed diabetes. Infection, myocardial infaraction, stroke, or recent surgery is the precipitating factors.

Clinical features

Clinical features are dehydration and stupor or coma due to hyperosmolality. Nausea, vomiting and abdominal pain are much less common because there is no acidosis. There is no hyperventilation as seen in DKA.

Investigations

- Severe hyperglycemia, blood sugar 600-2400 mg/dl but ketone bodies in urine are absent.
- Plasma osmolality >310 mosm/L.
- Serum bicarbonate > 15meq/L
- ABGs show normal pH.
- Normal anion gap (< 14 meq/L)

Table 7.11 Guidelines for the management of diabetic ketoacidosis

Time (hrs)	Insulin (use only short-acting (soluble) insulin)	Fluid (i.v.)	Potassium (i.v.)	Other
	Start i.v. insulin infusion 5 U/hr (Alternatively, 10–20 U i.m. followed by 5 U/hr i.m. thereafter)	Start i.v. 0.9% saline infusion, 1 litre in 30 min		Check capillary blood glucose. If ≥ 17 mmol/l obtain venous blood for urgent laboratory measurement of glucose, Na, K, Cl, CO_2, urea and pH or [H^+]. Test urine for ketones
0.5	Continue insulin 5 U/hr i.v.	0.5 litre of 0.9% saline in 30 min	If plasma K^+ > 5.5 mmol/l give no KCl; 3.5–5.5 mmol/l give 20 mmol KCl/l of infused fluid; < 3.5 mmol/l give 40 mmol KCl/l of infused fluid	If plasma Na^+ > 155 mmol/l give 0.45% rather than 0.9% saline until Na^+ falls to 140 mmol/l. If pH < 7.0 ([H^+] > 100 nmol/l) give 300–500 ml 1.26% sodium bicarbonate over 30 min into large vein
1	Continue insulin 5 U/hr i.v.	0.5 litre of 0.9% saline in 1 hr	As above	Recheck biochemistry
2	Continue insulin 5 U/hr i.v. (higher rate if fall in blood glucose < 3 mmol/hr)	0.5 litre of 0.9% saline in 2 hrs	As above	Recheck biochemistry
	When blood glucose < 15 mmol/l Reduce rate of insulin infusion to 1–4 U/hr	Change to 5% glucose infusion 0.5 litre/2 hrs	Continue i.v. K^+ supplements	Continue to check biochemistry every 2–4 hrs

Continue with regimen until fluid deficit replaced, ketonuria abolished and adequate oral intake of carbohydrate feasible.

N.B. These guidelines for a typical 'average' case should be modified appropriately in the individual patient after considering the blood biochemistry and clinical features, e.g. see below for information on treatment of non-ketotic hyperosmolar diabetic coma.

A Comparison of Diabetic Ketoacidosis and Hyperosmolar Nonketotic Syndrome

Feature	Diabetic Ketoacidosis	Hyperosmolar Nonketotic Syndrome
Age of patient	Usually <40 yr	Usually >60 yr
Duration of symptoms	Usually <2 days	Usually >5 days
Plasma glucose	Usually <600 mg/dL	Usually >600 mg/dL
Serum sodium	Normal or low (130–140 mEq/L)	Normal or high (145–156 mEq/L)
Serum potassium	Normal or high (5–6 mEq/L)	Normal (4–5 mEq/L)
Serum bicarbonate	<15 mEq/L	>15 mEq/L
Ketone bodies	Positive at $\geq 1:2$ dilution	Negative at 1:2 dilution
pH	<7.35	>7.3
Serum osmolality	Usually <320 mOsm/kg	Usually >320 mOsm/kg
Fluid deficit	$\leq 10\%$ body weight	$\leq 15\%$ body weight
Cerebral edema	Subclinical asymptomatic, rare clinically	Very rare
Prognosis	3%–10% mortality ($>20\%$ for people >65 yr)	10%–20% mortality
Subsequent course	Insulin therapy required in most cases	Insulin therapy not usually required

Treatment of hyperosmolar coma

Treatment of hyperosmolar non- ketotic coma is similar to ketoacidosis with some differences:

Fluid replacement

Fluid replacement is the mainstay of treatment in hyperosmolar coma. It can reduce hyperglycemia by correcting hypovolemia, which then increases both glomerular filtration and renal excretion of glucose. Saline should be of 0.45% NaCl (not 0.9% normal saline). As much as 4-6 liters fluid may be required in the first 8-10 hours. Once blood glucose reaches to 250mg/dl fluid replacement should include 5% dextrose water in either 0.45% or 0.9% saline.

Insulin therapy

Insulin may be required to reduce hyperglycemia but lesser in amount than required in ketoacidosis. Initial dose of 15 units IV and 15 units S/C of regular insulin is usually effective, with subsequent dose of 10-20 units S/C every 4- hours.

Potassium replacement

Less potassium replacement is required in hyperosmolar coma because there is no acidosis. However serum potassium may decline rapidly after giving insulin , it is advised to add potassium chloride (10 meq/L) to initial bottle of saline if serum potassium is not elevated.

Heparin

Heparin As the thromboembolic complications are common in hyperosmolar coma; prophylactic S/C heparin is recommended.

Prognosis

Mortality of hyperosmolar coma is more than 10 times that of ketoacidosis because of its higher incidence in old age who may have cardiovascular and other co-morbidities.

INFECTIONS IN DIABETES

Poorly controlled diabetes causes increased susceptibility to the following infections:

Skin

- Staphylococcal infections (boils, abscesses)
- Mucucutaneous candidiasis

Urinary tract

- Urinary tract infections
- Perinephric abscess

Lungs

- Staphylococcal and pneumococcal pneumonia
- Tuberculosis

The reason why poor control predisposes to infection is that chemotaxis and phagocytosis by polymorphonuclear leukocytes is impaired at high blood glucose levels.

VASCULAR DISORDERS IN DIABETES

Large vessel disease

Diabetes is a risk factor in the development of atherosclerosis mainly in large blood vessels; that is responsible for high incidence of stroke, myocardial infarction and foot gangrene.

Small vessel disease

In diabetes small blood vessels throughout the body are affected particularly at three sites.

- The retina – causing diabetic retinopathy
- The renal glomerulus – causing diabetic nephropathy.
- The nerve sheath – causing diabetic neuropathy, retinopathy, nephropathy.

DIABETIC NEUROPATHY

Mechanism

The hypothesis for mechanism of neuropathy are as follows:

- Occlusion of the vasa nervosum OR
- Hyperglycemia leads to increase formation of sorbitol and fructose in Schwann cells, accumulation of these sugars may disrupt the nerve function (causing delayed nerve conduction velocity) and nerve structure (causing segmental demyelination).

TYPES OF DIABETIC NEUROPATHY

Polyneuropathy

- Symmetrical, mainly sensory and distal.
- Asymmetrical, mainly motor and proximal.

Mononeuropathy

- Involvement of distribution of one nerve is called mononeuropathy.
- When single nerve of different areas is involved at the same time, this is called mononeuritis multiplex.

Autonomic neuropathy

- Cardiovascular
- Gastrointestinal
- Genitourinary
- Vasomotor pupillary

TYPES OF NEUROPATHY

- Symmetrical sensory polyneuropathy
- Asymmetrical motor neuropathy
- Mononeuropathy
- Autoimmune neuropathy

SYMMETRIC SENSORY POLYNEUROPATHY

(Very common complication of diabetes)

Symptoms

- Paraesthesia in the feet hands
- Dull pain in the lower limbs worse at night
- Burning sensation in the sole
- Sense of numbness in the feet

Signs

- Loss of tendon reflexes in the lower limbs
- Diminished perception of vibration sensation in distal parts
- Glove and stocking type impairment of other sensations
- Loss of deep pain and temperature sensation in the feet
- Cutaneous hyperesthesia (increased sensitiveness to pain)
- Painless ulcers on the feet, painless distal arthropathy characterized by disorganization of the joints (Charcot joints) (Sharkot joints)

There may be some motor involvement causing:

- Muscle weakness and wasting
- Toes may be clawed up due to wasting of the interosseus muscles

ASYMMETRICAL MOTOR NEUROPATHY

- This is sometimes called **diabetic amyotrophy**.
- Presentation is severe and progressive weakness and wasting of proximal muscles of lower (and occasionally upper) limbs.
- It is commonly associated with severe pain, mainly felt on the anterior aspect of the leg.
- Sometimes there is marked loss of weight (called neuropathic cachexia).
- Painful wasting is usually asymmetrical with extreme tenderness of the affected area.
- This condition is thought to involve acute infarction of lumbosacral plexus.
- There is loss of tendon reflexes on affected side.
- Sometimes there is extensor plantar response and CSF protein is raised.
- Recovery usually occurs within 12 months, some deficits become permanent and management is mainly supportive.

MONONEUROPATHY

- Involvement of distribution of one nerve is called mononeuropathy
- It may be motor (predominantly) or sensory involving peripheral or cranial nerve. Femoral and cranial nerves are commonly involved.
- Involvement of 3rd and 6th nerve resulting in diplopia due to impaired ocular movements is common.
- Carpal tunnel syndrome due to involvement of median nerve.
- Foot drop due to femoral, sciatic and lateral popliteal nerves involvement.
- Mononeuritis multiplex: When single nerve of different areas is involved at the same time, this is called mononeuritis multiplex.

AUTONOMIC NEUROPATHY

Either sympathetic or parasympathetic nerves may be predominantly involved.

Clinical features

Cardiovascular

- Postural hypotension
- Resting tachycardia
- Fixed heart rate

Gastrointestinal

- Dysphagia, due to oesophageal atony
- Abdominal fullness, nausea and vomiting, unstable diabetes due to delayed gastric emptying (gastroparesis)
- Nocturnal diarrhea and faecal incontinence
- Constipation due to colonic atony

Genitourinary

- Difficulty in micturition, urinary incontinence, recurrent infection, due to atonic bladder
- Impotence and retrograde ejaculation

Sudomotor

- Gustatory sweating
- Nocturnal sweats without hypoglycaemia
- Anhidrosis – fissures in the feet

Vasomotor

- Feet feel cold, due to loss of skin vasomotor responses.
- Dependent edema, due to loss of vasomotor tone and increased vascular permeability
- Bullous formation

Pupillary

- Decreased pupil size
- Resistance to mydriatrics
- Delayed or absent response to light

Loss of awareness of hypoglycemia

- Sympathetic or parasympathetic denervation and hypothalamic dysfunction results in loss of awareness of hypoglycemia. (Features of hypoglycemia are mainly mediated through sympathetic activity; when these nerves are impaired there is lack of symptoms development of hypoglycemia and hypoglycemic insult results without warning).

MANAGEMENT OF NEUROPATHIES

Neuropathy	Management
Painful neuropathy (pain and paraesthesia)	• Strict glycemic control • Tricyclic antidepressants e.g. imipramine, amitriptyline • Anticonvulsants (gabapentin, carbamazepine) • Antiarrhythmic (mexiletine)
Postural hypotension	• Support stockings • Fludrocortisone • NSAIDs
Gastroparesis	Metoclopramide, domperidone Erythromycin
Diarrhea	• Loperamide • Octreotide
Constipation	Laxatives
Atonic bladder	Intermittent self catheterization
Excessive sweating	Anticholinergics (propantheline)
Impotence	• Injection of prostaglandin E1 in carpus cavernosum of penis. • Sildenafil (Viagra) • Vacuum device • Implanted penile prosthesis • Psychological counseling

DIABETIC FOOT

There are three factors responsible for tissue necrosis in the feet of diabetic patients:

1. Neuropathy:
Necrosis occurs due to prolonged pressure. Patient does not feel pain due to sensory neuropathy, therefore if he/she gets injury, there is no feeling of pain resulting in negligence of wound care. This leads to tissue necrosis.

2. Ischemia
Ischemia occurs due to shunting of blood via peripheral arterio-venous anastomosis occurring in neuropathic feet, thereby reducing blood flow in the smallest vessels. Therefore there is reduced blood supply to the most peripheral tissues even when the circulation is apparently good.

3. Infection
Diabetic patient is more prone to have skin infection and there is decreased ability of wound healing which leads to necrosis.

DISTINGUISHING FEATURES BETWEEN ISCHAEMIA AND NEUROPATHY IN THE DIABETIC FOOT

Neuropathy	Ischemia
Symptoms • Paraesthesia • Pain • Numbness	*Symptoms* • Claudication • Rest pain
Structural damage • Ulcer • Sepsis • Abscess • Osteomyelitis • Digital gangrene • Charcot joint	*Structural damage* • Ulcer • Sepsis • Gangrene

Management

- Patient education to keep feet as clean as face. Avoid smoking and should not cut their own toe nails.
- Once the ulceration or gangrene has occurred, the aim is preservation of viable tissue. There are two main threats; infection and ischemia:

Infection:

- Early effective antibiotics.
- Drain if thee is collection of pus
- Regular foot X-rays to see bone involvement

Ischemia:

- Assess the blood flow to the feet clinically or with Doppler ultrasound.
- Cholesterol-lowering drugs are useful as adjunctive therapy when early signs of ischemia are detected.
- When chronic foot ulcers are refractory to standard debridement and antibiotics, platelet-derived growth factor should be considered for local application.
- Non-selective beta-blockers are relatively contraindicated in patients with ischemic foot ulcers; these drugs may reduce peripheral blood flow.

Indications of amputation

- Uncontrolled infection
- Osteomyelitis
- Extensive tissue destruction

MANAGEMENT OF DIABETIC FOOT ULCERS

- Remove callous skin
- Treat infection
- Avoid weight-bearing
- Ensure good diabetic control
- Control oedema
- Undertake angiogram to assess feasibility of vascular reconstruction in some cases

Diabetic foot: practice points

- Prevention is the most effective way of dealing with the problem of tissue necrosis in the diabetic foot
- A specialist chiropodist (podiatrist) is an integral part of the diabetes team to ensure regular and effective chiropody and to educate patients in care of the feet



DIABETIC NEPHROPATHY

Diabetic nephropathy is the most common cause of chronic renal failure. Patients with type 1 diabetes have a 30-40% chance of developing nephropathy after 20 years – in contrast to much less frequency in type 2 patients in whom 15-20% patients develop neuropathy. However, since there are many more individuals affected with type 2 diabetes, end-stage renal disease is much more prevalent in type 2 than in type 1.

The kidney may be damaged by diabetes in three main ways:

Diabetic glomerulosclerosis
Clinically nephropathy secondary to glomerular disease manifests 10-20 years after diagnosis. Structural abnormalities are the thickening of the glomerular basement membrane and disruption of protein cross-linkages that make the membrane as ineffective filter. As a result, a progressive loss of protein into the urine occurs starting from microalbuminuria and leading to frank proteinuria.

Ischemic lesions
Characterized by hypertrophy and hyalinization of the afferent and efferent arterioles.

Infective lesions
Infective lesions in kidneys occur as an ascending infection due to bladder stasis that results from autonomic neuropathy.

RISK FACTORS FOR DEVELOPING DIABETIC NEPHROPATHY

- Poor control of blood glucose
- Long duration of diabetes
- Presence of other microvascular complications
- Racial group (e.g. incidence high in Asian races, Pima Indians)
- Pre-existing hypertension
- Family history of diabetic nephropathy
- Family history of hypertension

STAGES OF NEPHROPATHY

- Initially there is microalbuminura
- Microalbuminuria leads to progressive diabetic nephropathy manifesting as heavy proteinuria (nephrotic syndrome) and renal failure with raised urea and creatinine.

Microalbuminuria

- Microalbuminuria can be detected by 24-hour urinary proteins or overnight urine collection or analysis of albumin-creatinine ratio in early morning spot urine collected upon awakening.
- Normal person excretes less than 15 μg/min during over night urine collection; values more than 20 μg/min or higher should be considered abnormal microalbuminuria.
- In the early morning spot urine, a ratio of albumin (μg/L) to creatinine (mg/dl) of <30 μg/mg creatinine is normal, and a ratio of 30-300 μg/mg creatinine suggests abnormal microalbumunuria. At least two of three overnight or early morning spot urine collection over a 3-6 month period should be abnormal for the diagnosis of microalbuminuria.
- Increased microalbuminuria correlates with increased level of blood pressure and increased LDL cholesterol leading to increased incidence of cardiovascular deaths even in the absence of renal failure.
- Glycemic control as well as low-protein diet (0.8 g/kg/d) and ACE inhibitors (even in normotensive patient) may reduce microalbuminuria and progression to nephrotic syndrome.

Progressive diabetic nephropathy
It manifests as nephrotic syndrome (heavy proteinuria, hypoalbuminemia, hyperlipidemia, edema) and progressive renal insufficiency. In contrast to other renal disorders, the proteinuria associated with diabetic nephropathy does not diminish with progressive renal failure.
Hypertension develops with progressive renal involvement, coronary and cerebrovascular atherosclerosis is accelerated.

INVESTIGATIONS

- Urine D/R detects albumin
- 24 hours urinary proteins and creatinine clearance.
- Albumin – creatinine ratio in early morning spot urine.
- Urine culture
- Ultrasound kidney

MANAGEMENT

1. Low protein diet (0.8 g/kg/d): low protein diet causes decreased protein filtration and less nephrosclerosis.
2. Salt restriction if edema is present.
3. Energetic treatment of hypertension reduces the rate of disease progression. Target blood pressure is 140/90. ACE inhibitors are the drugs of first choice, because they control blood pressure as well as reduce proteinuria by reducing efferent arteriolar pressure of glomeruli.
4. Loop diuretics e.g. Frusemide in case of edema.

   The drugs which should be avoided:
   - Thiazide diuretics: They inhibit insulin secretion, therefore raise the blood glucose level in NIDDM.
   - Beta-blockers: They aggravate peripheral vascular disease and impotence.

5. Insulin sensitivity increases in renal failure (because insulin is inactivated by kidney; in case of renal failure insulin is not inactivated completely and continues glucose lowering effect. Therefore dosage of insulin should be reduced.
6. Oral hypoglycemic drugs should be avoided if renal impairment develops; especially metformin should not be used since the risk of lactic acidosis increases with impaired renal function. If oral hypoglycemics are used then select the drug that is excreted through or metabolized by the liver such as glipizide (Minidiab) or gliclazide (Diamicron).
7. Dialysis required for end-stage renal disease, renal transplantation may improve the life. A segmental pancreatic graft transplantation performed at the same time as a renal transplantation may give the patient a year or so of freedom from insulin injection.

DIABETIC RETINOPATHY

Diabetic retinopathy occurs with the duration of diabetes 10-20 years. Diabetes causes increased thickness of the basement membrane and increased permeability of the retinal capillaries. Aneurysmal dilattion may occur in some vessels. Following are the changes occurring in retinopathy. Up to 20% patients with type 2 diabetes have retinopathy at the time of diagnosis of diabetes. Other ocular lesions frequently occur in diabetics are early development of cataract due to non-enzymatic glucosylation of lense protein, and development of glaucoma.

Background retinopathy characterized by:
- Dot hemorrhage: due to capillary microaneurysms
- Blot hemorrhage: due to leakage of blood into deeper layers of retina
- Hard exudates: exudate rich in lipids and protein having bright yellow white color

Background retinopathy does not itself constitute a threat to vision but may progress to two other forms of retinopathy:
- Maculopathy
- Proliferative retinopathy

Diabetic maculopathy characterized by:
- Hard exudates arranged in horse shoe or circular fashion around the central and lateral part of macula. This may cause loss of visual acuity by occluding central part of retina.
- Edema and ischemia of macula may also occur.

Proliferative retinopathy characterized by:
- *Cotton-wool spots* (soft exudates): representing patches of retinal edema.
- *Neovascularization:* New vessel formation lying superficially and growing forward into the vitreous. These vessels are fragile and rupture easily causing vitreos hemorrhage. Ophthalmoscopy gives appearance of a featureless gray haze.

MANAGEMENT

General measures

1. Control hypertension and avoid smoking.
2. Good glycemic control.
3. Annual consultation with ophthalmologist should be arranged. Patients with macular edema, severe non- proliferative or proliferative retinopathy require the care of ophthalmologist.
4. Ophthalmoscopy is essential in the following conditions:
   - Long duration of DM
   - Poor control
   - Pregnancy
   - Use of oral contraceptives
   - Heavy smoking
   - Neuropathy and nephropathy

Specific

- Background retinopathy: No medical treatment only general measures.
- Maculopathy and prolifertie retinopathy: treatable by retinal photocoagualtion with lasers (laser therapy) by opthalmologist..

GESTATIONAL DIABETES

Gestational diabetes is defined as hyperglycemia diagnosed for the first time in pregnancy. It occurs in individuals who have an inherited predispostion to develop diabetes and may take the form of either type 1 or type 2 diabetes.

Gestational diabetes is associated not only with increased rate of perinatal morbidity and neonatal mortality but also with high incidence of subsequent diabetes in mother.

A screening procedure is measurement of fasting blood sugar and one hour after 50g oral glucose load. While 100-g glucose is given for diagnostic purpose.

Screening and diagnostic criteria for gestational diabetes

Plasma glucose	50-g screening test mg/dl	100-g diagnostic test mg/dl
Fasting	-	95
1h	140	180
2h	-	155
3h	-	140

TREATMENT

- Treatment is with diet modification and insulin. Insulin does not cross placenta while oral hypoglycemic agents cross placenta and therefore contraindicated.
- Gestational diabetes does not increase the risk of congenital abnormalities.
- Not all diabetes in pregnancy are gestational diabetes, true type 1 diabetes may first time appear during pregnancy.

Obstetric problems associated with diabetes

Poorly controlled diabtes is associated with stillbirth, large sized fetus causing mechanical problems in delivery, hydromnios and pre-eclampsia. Ketoacidosis in pregnancy carries a 50% risk of fetal morality.

Neonatal hypoglycemia may develop, because hyperglycemia that crosses placental stimulates increased amounts of insulin in fetus, after delivery insulin remains high but now baby is not exposed to high blood glucose, therefore hypoglycemia develops.

OBESITY

The collection of an excessive amount of body fat is termed as obesity.

ETIOLOGY

The accumulation of excessive fat results from imbalance between energy intake and its utilization. The factors which take part in the development of the obesity are as follows:

Age:
At middle aged people have more tendency to become obese. Anyhow, obesity is present among all age groups.

Sex:
Female have greater tendency to gain weight particularly at puberty and during pregnancy.

Profession:
Persons belong to certain professions have "weight gain" tendency more than others. These are cooks, barmen and whose nature of job is secondary i.e.

Socio-economic condition
Obesity has been found more among lower socio-economic groups in western countires in contrast to this world, where prosperous people are more obese.

Endocrine disorders
Certain diseases of endocrine glands are associated with obesity i.e. hypothyroidism, Cushing's disease, hypogonadism and hypopituitarism.

Hereditary
Persons from certain families show increased tendency to gain weight. After this observation a genetic predisposiion has been postulated. Anyhow, no gene has been found responsible for obesity until now.

Eating habits
Increased eating tendency is not always owing to polyphagia. This may be influenced by external factors i.e. availability, advertisement, smell, taste and appearance of food. Certain persons under pscychological upset, eat more i.e. during depression.

Drugs
Use of certain drugs, such as steroids, phenothiazenes, oral contraceptives and insulin, lead to obesity.

CLINICAL PRESENTATION

Obese people come to the doctor not only to complain about their fitness but also with problems. This may present with exertional dyspnoea, pain in back, hypertension, diabetes mellitus, or I.H.D.

DIAGNOSIS

Diagnosis of obesity is established by general appearance and recording of height and weight. The height and weight of the patient is compared with standard "height-weight" charts. Another test to diagnose obesity is to measure the thickness of skin of triceps muscle. Reading more than 20 mm in males and 28 mm in females indicates obesity.

DIFFERENTIAL DIAGNOSIS

Obesity must be differential from other causes of weight gain i.e. edema due to any other cause.

COMPLICATIONS

Obese persons suffer from following disorders:

Cardiovascular Disorders:
Obesity puts an extra-load on the heart. There is increased cardiac output, and stroke volume. Blood pressure is raised. Patient becomes more prone to develop I.H.D.

Mechanical disorder:
Obese patiens are just carrying an extra load of fat, which adversely affects the weigh bearing joints of body. Patient develops the flat feet and degenerative changes of hip joints, knee joins and lumbosacral vertebrae. Leg muscles fail to push the venous blood back to the heart effectively. Increased load on abdominal wall and diaphragm causes hernia formation. Increased weight of body makes the respiration labored and person develops exertional dyspnea.

Metabolic disorder:

Obese person develops non-insulin dependent diabetes. The blood level of cholesterol and triglycerides increased. Patient may develop gout due to hyperuricemia. Gallstones are more common among fatty people.

Psychological disorder

Obesity makes a person psychologically upset. They are being criticized by each person for their over weight. The behavior of the society causes psychological disorders in term i.e. anxiety and depression particularly among females.

Life expectancy:

Persons with 30 percent over weight have 30% more mortality rates. Those who are 40% over weight have 50% more mortality than the normal persons.

TREATMENT

Before starting the treatment patient should be told that ultimate responsibility lies on him. The job of doctor is just to advise and supervise. Unless patient acts upon the advice with his/her own will, there is no way to make him/her slim.

The treatment of obesity depends upon two important factors.

- To reduce the energy input
- To increase the energy output.

Reduction of the energy input:

Total daily energy intake should be between 800 to 1600 Kcal depending upon the age, sex and job of the person. A housewife of moderate obesity needs 1000 Kcal/day while a young man doing active physical job, needs about 1500 Kcal/day. The patients are given balanced diet which comprises of proteins, CHO and fats. Along with these basic elements, care is taken to provide sufficient amount of vitamins and minerals.

Proteins

Daily intake of proteins should be about 55 gm. Source of protein should be both red and white meat i.e. mutton, beef and chicken. Eggs are also given.

Carbohydrate

Per day 100gm of CHO are required. CHO is taken in the form of whole grain cereal and vegetables. This source will not only provide CHO, but dietary fiber also. Fruits are also taken as source of CHO. Pure form of sweets is avoided.

Minerals

Iron and calcium are two important minerals which must be supplemented. Milk is a rich source of calcium which should be part of daily diet, while iron is given separately in the form of tablets or capsules.

Vitamins

Intake of green vegetables and fruits, not only give a bulk to the diet, but also provide vitamins i.e. vitamin A, C and B complex. Taking of eggs, meal and fish provides other vitamins. Intake of methylcellulose of full stomach, so patient eats less. Methylcellulose itself has not nutritional value. Patient is advised not to take "Cola" drinks. It is better to avoid alcohol. Extra eating should be discouraged.

Increase in energy output

Energy output is increased by doing physical work i.e. exercise. Best exercise, irrespective of age, is walking. Walking at a speed of 3 miles/hour will spend our 240 Kcal. Other exercises are gardening, swimming, jogging and yoga. While advising to the paitent about exercise, it is kept in mind that his physical activities should not exceed his cardiovascular capacity. Patients who fail to respond to above-measures are hospitalized and under strict control above mentioned regimen is followed.

Starvation therapy:

Certain resistant cases are given "starvation therapy" i.e. for several weeks, they are given nothing but water, minerals and vitamins. Patient develops ketosis and hyperuricemia as side effect of prolonged starvation.

Drugs:

Amphetamines are used as anorectic drugs. As these drugs are addictive, so should be used intermittently. Hypertensive and IHD patients should not be advised to use these drugs.

یہ کلوریز مختلف غذاؤں کے 100 گرام میں ہوتی ہیں——

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انڈے کی سفیدی	37
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کچھوے کا انڈا	124
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راہو مچھلی	97
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شارک مچھلی	93
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ڈبل روٹی	244
چینی	398
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آمچور	337
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کوکا کولا، پیپسی (فی بوتل)	110
فانٹا، مرنڈا (فی بوتل)	130

SURGICAL TREATMENT

To very resistant cases following surgical procedures are advised:

1. **Wiring of the jaws**
   The jaws are wired so that patient could only take liquid diet.
2. **Stapling of stomach**:
   Stomach size is reduced by stapling a portion of stomach. This is reversible proceess.
3. **Intestinal bypass**:
   Operation is due to bypass the small intestine. This procedure results in malabsorption syndrome.

Prognosis

Loss of 5 kg of weight is easy. More than this needs lot of patience and strict compliance by the patient.

METABOLIC DISEASES

AMYLOIDOSIS

Amyloidosis is a disorder of protein metabolism in which there is an extracellular depositon of pathologic insoluble fibrillar proteins in organs and tissues.

TYPES

1. Primary amyloidosis

It is a plasma cell dyscrasia related to multiple-myeloma and non-Hodgkin's lymphoma. Nephrotic syndrome is often the presenting feature. There may be the involvement of heart (causng restrictive cardiomyopathy, arrhythmias), involvement of gut presents with malabsorption and tongue involvement presents with macroglossia. Median survival is 2-3 years.

2. Secondary amyloidosis

In this type the protein deposited is a normal serum protein which is an acute phase reactant that is produced in the liver in response to inflammation. The most common causes are rheumatoid arthiritis, tuberculosis, leprosy, bronchiectasis, and osteomylitis.

Nephrotic syndrome progressing to renal failure is often the first manifestation. Hepatosplenomegaly is common. Treatment require reduction of inflammation and treatment of infection.

3. Family amyloidisis

It is an autosomal dominant disease where the mutant protein forms amyloid fibrils starting using in middle age.

4. Amyloidisos in chronic dialysis patients

DIAGNOSIS

Amyloidosis is best diagnosed by biopsy of the affected organ. Biopsy of buccal mucosa or abdominal fat may be suggestive.

TREATMENT

There is no treatment for amyloidosis, just treatment of associated disorder and management of complications (such as nephritic syndrome) can be offered.

PORPHYRIA

It is a group of inborn error of metabolism caused by abnormalities of enzymes involved in the biosynthesis of haem, resulting in overproduction of intermediate compounds called porphyrins.

In porphyria the excess production of porphrins occurs either in the liver (hepatic porphyries) or the bone marrow (erhtyropoietic porphrias). Porphyrias can also be divided according to clinical presentation as acute or subacute.

The classification of porphyrias

	Hepatic	*Erythropoietic*
Acute	Acute intermittent porphria Variegate porphyria Hereditary	
Sub-acute	Porphria cutanea tarda	Congenital porphyria Erythropoietic protoporphria

ACUTE INTERMITTENT PORPHRIA

This is an autosomal dominant disorder caused by deficiency of porphobilinogen deaminase activity leading to increased excretion of aminolevulinic acid and prophobilinogen in the urine. It mainly involves nervous system. Presentation is around 30 years of age, women are more affected than men. Precipitating factors may be alcohol, sulfonamides, barbitrates, other drugs and oral contraceptives.

Clinical features

It presents with:

- Intermittent abdominal pain that may simulate acute abdomen and leads to exploratory laparotomy. Sice the origin of pain is neurologic (due to abnormalities in autonomic innervation of gut) there is absence of fever and leukocytosis. There is complete recovery between attacks. Vomiting and constipation are also common.
- Any part of the nervous system may be involved with autonomic and peripheral neuropathy. Peripheral neuropathy may be symmetric or asymmetric and may lead to qudriplegia or respiratory paralysis.
- Hypertension and tachycardia
- Seizures and psychiatric disorders such as depression, anxiety and frank psychosis may occur.

Investigations

- Hyponatremia
- The freshly voided urine is normal in color, however it may turn black upon standing in light and air.
- Diagnosis may be confirmed by increased porphobilinogen in urine during attack.

Management

- Management is supportive, a high carbohydrate is maintained with intravenous glucose. Narcotics for pain.
- *Hematin* intravenous infusion 4mg/kg once or twice daily also appears to be of benefit. Sideeffects are phlebitis and coagulopathy.
- Screening of other family members should be done with the measurement of erythrocyte porphobilinogen and ALA synthetase.

PORPHYRIA CUTANEA TARDA

Patient presents with bullous eruption on exposure to sunlight; the eruption heals with scarring. Alcohol is the main precipitating factor.

RENAL DISEASES 6

FUNCTIONS OF KIDNEY

Excretory
Excretion of waste products and drugs

Regulatory
Control of body fluid volume and composition

Endocrine
Production of erythropoietin, rennin and prostaglandins

Metabolic
Metabolism of vitamin D, small-molecular-weight proteins

RENAL FUNCTION TESTS

GLOMERULAR FILTRATION RATE (GFR)

The GFR provides a useful index of overall renal function. It measures the amount of plasma ultrafiltered across the glomerular capillaries and correlates well with the ability of the kidneys to filter fluids and various substances. Daily GFR is in the range of 100-120 ml/min.

A low GFR is an evidence of serious progressive renal disease and indicates a decrease in total functioning renal mass. The GFR reduces in both acute and chronic renal failure.

GFR can be estimated by the creatinine clearance by the following formula:

$$C = \frac{U \times V}{P}$$

C: Creatinine clearance
U:Urinary creatinine mg/dl
P: Plasma creatinine mg/dl
V: Urine flow rate ml/min

Decreased GFR manifests as raised serum urea and creatinine. However serum urea and creatinine are not elevated above the normal range until there is a reduction of 50-60% in the GFR. Therefore it should be noted that normal urea and creatinine levels do not rule out renal insufficiency and when serum urea and creatinine begin to rise, more than 50-60% of renal damage has occurred.

SERUM UREA

Urea is produced in the liver and is the end product of protein catabolism. Urea is freely filtered by the glomerulus and about 30-70% is reabsorbed in the nephrons. *Dehydration causes increased urea reabsorption*. Therefore urea level increases during dehydration such as in acute diarrhea while the renal function is preserved and creatinine is normal. A normal urea to creatinine ratio is 20:1. This ratio is increased in dehydration while the ratio remains same in renal insufficiency. There are other factors that affect serum urea levels such as following:

Increased serum urea independent of GFR

- Dehydration
- Catabolic state
- High protein diet
- Glucocorticoids
- Tetracycline

Decreased serum urea independent of GFR

- Liver disease
- Malnutrition
- Low protein diet
- Old age

SERUM CREATININE

- Creatinine is the most useful clinical test in assessing progression of renal failure. However at least 50% of renal function is lost before rising serum creatinine. Therefore normal level of creatinine does not rule out impairment of renal function.
- Serial estimation of serum creatinine provides the best indication of state of renal function in patient with CRF.
- Creatinine is the product of muscle metabolism. It is freely filtered and not reabsorbed, however small amount is eliminated by tubular secretion that increases with dehydration overestimating the GFR.

Increased serum creatinine independent of GFR

- Ketoacidosis
- Drugs:cephalothin, cefoxitin aspirin, cimitidine, trimethoprim

Decreased serum creatinine independent of GFR

- Advanced age
- Liver disease
- Cachexia

URINALYSIS (URINE D/R)

- Colour
- Volume
- Specific gravity
- Reaction
- Glucose
- Ketones
- Protein
- Microscopy

Colour of urine	
Normal	Ranges from colorless to deep yellow depending on the concentration of the urochrome pigment.
Red	Blood, hemoglobulinuria, myoglobinuria, beetroot (chukandar)
Orange	Rifampicin
Yellow	Concentrated urine (e.g. dehydration, jaundice, B Complex, sulfasalazine)
Green	Methylene blue
Black	Severe hemoglobinuria, methyldopa
Brown	Bilirubin, phenothiazides

Volume

- Normal: 800 – 2500 ml/day.
- Oliguria: urine volume < 300 ml/day
- Anuria: urine less than 100 ml/day

Specific gravity

- It varies with the quantity of urine.
- Normal range 1.002 to 1.025
- Estimation required in investigation of polyuria or SIADH.
- Persistently low specific gravity suggests chronic renal failure or diabetes insipidus.
- High specific gravity suggests dehydration or diabetes mellitus with presence of large amount of glucose in the urine.

Reaction

Fresh urine is acidic with an average pH 6. The pH is important in investigation and management of renal tubular acidosis. Distal tubular acidosis should be suspected if the early morning urine is consistently alkaline and cannot be acidified. Infection with urea-splitting proteus micrabilis can cause urine alkaline that favors renal calcium stone formation.

Glucose

Glucose in urine usually indicates diabetes but it may occur in impaired renal tubular ability to absorb glucose (renal glycosuria) such as in Fanconi's syndrome. False positive or negative results may occur if patient is taking large doses of vitamin C or taking tetracycline or levodopa.

Ketones

Ketones in the urine of diabetic patient is an important indication of diabetic ketoacidosis. Ketone may be present in urine due to starvation.

Protein

Causes of proteinuria are discussed in the next section. Normal protein loss from urine is less than 150 mg/24 hours.

Microscopy

White cells:

More than 10 or more WBC per cm indicate UTI (mostly) but it may also present in patient with stones, tubulointestinal nephritis, tuberculosis, papiliary necrosis.

Red cells:

Presence of 2-5 RBC per high power field indicates positive test for hematuria and can be detected on dipstick. Red cells may come from glomeruli or below. RBCs of glomruli origin tend to be dysmorphic and have many sizes and shapes whereas RBCs of non glomeruli origin are uniform in size and shape.

Casts

These are cylindrical structures that form within the kidney tubules by the coagulation of proteins.

- Hyaline cast: concentrated urine, fever, diuretic therapy, after exercise.
- Granular cast – found in chronic glomerulonephritis, diabetic nephropathy & malignant hypertension.
- White cell cast found in acute pyelonephritis.
- Red cell cast found in glomerulonephritis.
- Epithelial cast found in acute tubular necrosis, interstitial nephritis.
- Broad waxy cast is found in chronic renal failure.

Crystals

- *Uric acid:* in acidic urine, hyperuricosuria, acute uric acid nephropathy.
- *Calcium phosphate:* in alkaline urine.
- *Calcium oxalate:* hyperoxaluria, acid urine.
- *Cystine:* cystinuria

IMAGING TECHNIQUES

ULTRASOUND

It is useful in detecting:

- Renal size: kidneys less than 10 cm are considered small.
- Hydronephrosis
- Renal mass
- Polycystic kidney

PLAIN X-RAY ABDOMEN

- Renal calcification or radiodense calculi
- Outline of ureters & bladder

RADIONUCLIDE STUDIES

^{99m}Tc-DTPA

- It is used to access GFR when urine collection is difficult or expected inaccurate.
- Helpful in the diagnosis of renal artery stenosis.
- Localizes the site of obstruction.

^{99m}Tc-DMSA

- It determines the contribution of each kidney to overall renal function.
- It localizes infection such as renal abscesses or infection within a renal cyst.

CT SCAN

CT scan shows kidneys, ureters and surrounding tissues in detail and is useful in the diagnosis of renal tumors.

MRI

MRI is helpful in differentiation between cystic and solid renal masses. MR angiography of renal arteries in increasingly used to screen for renal arterial disease.

ARTERIOGRAPHY AND VENOGRAPHY

Conventional or digital subtraction angiography are used. The latter allows the use of smaller doses of contrast medium which can be injected via a central venous catheter or via a fine transfemoral arterial catheter.

Arteriography is mainly used to define extrarenal or intrarenal arterial disease and the presence and extent of renal tumors.

Venography is used to exclude renal vein thrombosis.

EXCRETION UROGRAPHY (IVP OR IVU)

- Size and outline of the kidney (small size indicates chronic renal disease)
- Size, shape and disposition of calyces and pelvis for evidence of calyceal clubbing, abnormal dilatation, cavitation or filling defect.

ANTEGRADE UROGRAPHY

This involves percutaneous puncture of renal calyx, with insertion of a fine catheter and infection of contrast medium in an antegrade fashion and the X-rays are taken. This test demonstrates the site of obstruction of upper urinary tract.

RETROGRADE UROGRAPHY

Following cystoscopy, a catheter is passed a short distance up in the ureter and contrast medium is injected, followed by X-ray filming. It demonstrates obstruction in lower urinary tract. It is now rarely performed.

MICTUARATING CYSTOUROGRAPHY

This involves catheterization and the instillation of contrast medium into the bladder. The patient is then screened and filmed during voiding to demonstrate or exclude vesicouretric reflux and to study bladder emptying.

RENAL BIOPSY

Indications

- Adult nephritic syndrome
- Persistent proteinuria > 1 g/24 hours
- Adult acute nephritic syndrome
- Persistent microscopic or macroscopic hematuria (disordered haemostasis excluded)
- Systemic disease with renal involvement such as sarcoidosis and amyloidosis.
- Chronic renal failure with normal or near normal sized kidneys.
- Unexplained acute renal failure.
- Childhood nephritic syndrome, if significant hameaturia present or unresponsive to corticosteroid therapy.
- Childhood acute nephritic syndrome, if significant urinary abnormalities persist for longer than 12 month or renal functional impairment present.

Contraindications

- Disordered coagulation
- Thrombocytopenia
- Uncontrolled hypertension
- Solitary kidney (except in transplanted kidneys)
- Small contracted kidneys, i.e. less than 60% of expected bipolar length because it is technically difficult, histology hard to interpret and prognosis cannot be altered.
- Uncooperative patient

Complications

- Pain
- Infection
- Bleeding into urine that may be massive and form clot leading to urinary obstruction.
- Bleeding around the kidney.

Practical

Before biopsy

- A coagulation screen is performed. It must be normal.
- The serum is grouped and saved for crossmatching.
- The patient is given a full explanation of what is involved.

During biopsy

- The patient lies prone with a hard pillow under the abdomen.
- The kidney is localized by ultrasound.
- Local anaesthetic is injected along the biopsy track.
- The patient holds a breath when the biopsy is performed.

After biopsy

- A pressure dressing is applied to the biopsy site and the patient rests in bed for 24 hours.
- The fluid intake is maximized to prevent clot colic.
- The pulse and blood pressure are checked regularly.
- The patient is advised to avoid heavy lifting or gardening for two weeks.

COMMON URINARY SYMPTOMS

Urinary symptoms are very common and patients will come to your clinic with symptoms or bringing abnormal reports for your expert opinion. Therefore you should be aware of how to interpret the reports and how to proceed further.

POLYURIA

Persistent large increase in urine output is called polyuria. It must be differentiated from increased frequency of micturition in which there is passage of small amount of urine with increased frequency. Urine output more than 3 liters /day is usually defined as polyuria..

It is very important to decide whether the polyuria is due to free water excretion or due to excessive solute excretion (solute may be glucose, urea, electrolytes, mannitol).

Free water excretion

If the urine is dilute (osmolality <250 mosmol/L; it represents cause is either polydypsea or diabetes insipidus (central or nephrogenic).

Excessive solute excretion

If urine osmolality is more than 300 mosmol/L then cause of polyuria is excessive solute excretion such as:

- Glycosuria in uncontrolled diabetes mellitus.
- Mannitol administration
- High protein diet causing increased urea production and excretion.
- Excessive sodium loss in cystic renal diseases, Barter's syndrome, renal tubular damage.

(<u>Bartter's syndrome:</u> polyuria due to excessive urinary potassium loss resulting in hypokalemia, and hypotension as a result of increased aldosterone secretion). Asked in previous MCQs paper.

Investigations and management are according to the clinical situations.

INCREASED FREQUENCY OF MICTURITION

Frequent passage of small volumes of urine without an increase in total volume is called increased frequency of micturition.

Causes

- *Renal*: pyelonephritis
- *Ureter*: stone
- *Bladder:* cystitis, stone
- *Prostatate:* prostatitis, BPH
- *Urethera:* urethritis
- *Gynecological:* vaginitis, pregnancy
- *Psychological:* depression, tension.

PROTEINURIA

A normal individual excretes less than 150 mg/day of protein. A finding of over 150 mg/24 hours of protein is the criterion of proteinuria. Heavy proteinuria > 1g/dl indicates glomerular origin while mild to moderate proteinuria may develop due to tubular defect, functional cause or overproduction of circulating filterable plasma proteins. Causes of proteinuria are as following:

Primary renal diseases

Glomerulonephritis (different types)

Secondary renal disease

- *Systemic diseases:* diabetes, hypertension, and amyloidosis.
- *Drugs:* captopril, penicillamine, heroin, NSAID.
- *Infections:* hepatitis B, infective endocarditis, malaria, AIDS.
- *Allergy:* Vaccine, bee sting.

Functional proteinuria

Proteinuria develops due to some stresses and there is no renal disorder. Proteinuria is typically under 1 g/d. Causes are exercise, fever, severe hypertension, CCF, burns, postoperative and acute alcohol abuse.

Ortostatic proteinuria

Proteinuria which occurs when a patient is standing but not when recumbent is called orthostatic proteinuria. It is benign condition usually occurring below the age of 30.

Isolated proteinuria

When proteinuria develops without red blood cells or other formed elements in the urinary sediments, it is characteristic of some renal diseases that manifest little or no inflammatory reaction within the glomeruli is called isolated proteinuria. Causes are diabetes mellitus and amyloidosis.

Overload proteinuria

It results from production of excessive amounts of filterable proteins such as Bence- Jones proteins in multiple myeloma, myoglobinuria in rhabdomyolysis.

Tubular proteinuria

It results from inability of damaged tubules to reabsorb normally filtered proteins. Causes are acute tubular necrosis, toxic injury, drug induced interstitial nephritis, Wilson's disease, Fanconi's syndrome.

Microalbuminuria

Normal person excrete < 30 microgram of albumin per minute while the dipstick can detect albumin only when its concentration is more than 100 mg/L. Albumin excretion > 20 μg/min or 30-300 mg/24h is called microalbuminuria. Its significance is that it is an early indicator of diabetic nephropathy.

EVALUATION OF PATIENT WITH PROTEINURIA

First of all quantity proteinuria by either the following two methods:

24- hour urinary proteins

24- hours urinary collection: finding of > 150 mg/24h is abnormal and > 3.5 g/24h is in nephritic range.

Albumin- creatinine ratio

Ratio of urinary protein concentration to the urinary creatinine concentration in a early morning spot urine sample. 30 mg of albumin per gram of creatinine is considered abnormal. It is simple but less accurate method.

Renal biopsy

Renal biopsy is advised if proteinuria is associated with renal insufficiency particularly if it is acute in onset.

Management

- Reducing proteinuria may also reduce progression of renal disease. ACE inhibitors and angiotensin II receptor blockers reduce glomerular capillary pressure by reducing efferent artiolar resistance and reduce proteinuria.
- Low protein diet.
- Treatment of underlying cause.

HEMATURIA

CAUSES

Hematuria may be due to renal or extra-renal cause.

Renal causes

Renal causes may be glomerular or nonglomerular in origin.

Glomerular causes

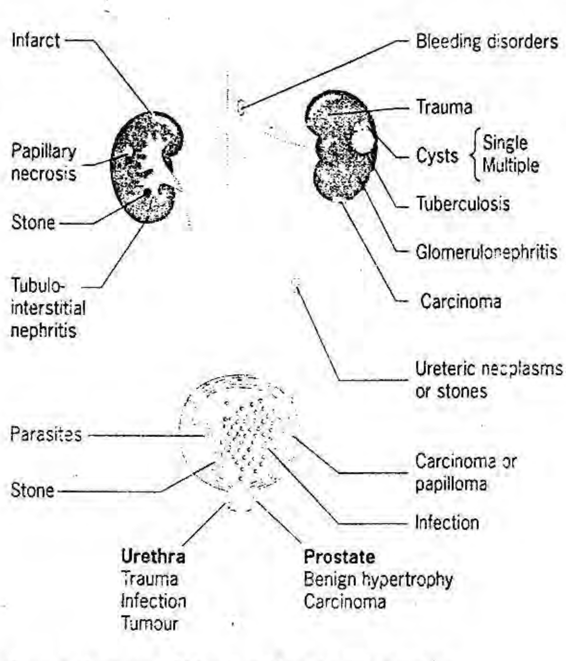
- IgA nephropathy
- Nephritic syndrome
- Post- streptococcal glomerulonephritis
- Membranoproliferative glomerulonephritis.

Non- glomerular causes

- Renal cysts (polycystic kidney)
- Renal stones
- Interstitial nephritis
- Renal tumors

Extra- renal causes

- *Ureter:* Stone, papilloma
- *Bladder:* Trauma, stone, hemorrhagic cystitis, papilloma, carcinoma.
- *Urethra:* Trauma, infection, tumors, stone
- *Blood disorder:* Purpura
- *Diabetes and sickle cell trait or disease* (causing papillary necrosis)
- *Drugs:*
  - Anticoagulants
  - *Analgesic abuse (causing papillary necrosis)*
  - *Cyclophosphomide (chemical cystitis)*
  - *Antibiotics (causing interstitial nephritis)*



Sites and causes of bleeding from the urinary tract

Sites and causes of bleeding from the urinary tract

Gross hematuria

Gross hematuria is usually non –glomeular in origin. In the absence of infection gross hematuria from a lower urinary tract is most commonly due from transitional cell carcinoma of bladder.

- Blood in start of voiding comes from urethra
- Blood diffusely present throughout the urine comes from the bladder or above.
- Blood only at the end of micturition suggests bleeding from prostate or bladder base.

Microscopic hematuria

- Glomerulonephritis
- Renal T.B.
- Collagen disease e.g. SLE
- Malignant hypertension
- Blood disorders
- Infective endocarditis
- Benign prostatic hyperplasia.
- Polyarteritis nodosa
- Goodpasture's syndrome
- Wegener's granulomatosus
- Alport's syndrome (hereditary nephritis)

Recurrent hematuria

- IgA nephropathy
- Alport syndrome tumors

INVESTIGATIONS

Urine analysis: proteinuria and cast suggest renal in origin, urine culture and sensitivity, urinary cytology, IVP, cystoscpy, ultrasound kidneys and ultrasound abdomen.

CONDITIONS WHICH MAY MIMIC HEMATURIA

- **Hemoglobinuria:** urine gives a positive chemical test for hemoglobin, but no red cells are detectable
- **Myoglobinuria:** no red cells are seen, but chemical tests for hemoglobin are positive. Myoglobin can be distinguished by spectrometry.
- **Acute intermittent porphyria**: fresh urine appears normal, but on standing for some hours a dark red color develops.
- Beetroot, senna, dyes used to color sweets and phenolphthalein may also mimic hamaturia.

URINARY RETENTION

CAUSES

Mechanical

- Bladder: Stone, papilloma, pressure from outside by retroverted gravid uterus.
- Prostate: B.P.H., Prostatis, malignancy, stone
- Urethra: Stricture, foreign body, urethritis

Nervous

- Disease of spinal cord & nerve roots e.g. fracture and dislocation of vertebra
- Spasmodic: Following operation of abdomen, perineum & scrotum
- Drugs: Anti-depressants, antihistamines

GLOMERULONEPHRITIS

This is a group of disease in which the disease affects the glomerulus and is often inflammatory in nature. The disease is immunologically mediated and involves both kidneys symmetrically.

It may be primary when major problem starts in the glomerulus or secondary when involvement is part of systemic disease such as in SLE.

GLOMERULAR DISEASE

Primary

- Minimal change glomerular disease
- Membrenous glomerulonephritis
- Membranoproliferative glomerulonephritis
- IgA nephropathy
- Crescentric (Goodpasture's Syndrome)
- Focus segmental glomerulonephritis

Secondary

Common

- SLE
- Polyarteritis nodosa
- Diabetes mellitus
- Amyloidosis
- Henoch Schontein disease
- Malarial nephropathy

Uncommon

- Pre-eclampsia
- Eclampsia
- Malignancy associated Paraproteinamea
- Cryoglobulinaemia
- Sarcoidosis
- Rheumatoid arthritis
- Scleroderma
- Hemolytic uremic syndrome
- Wegner's granulomatosus
- Cystomegalovirus nephropathy
- AIDS nephropathy

PATHOGENESIS

The two main processes are involved in the pathogenesis of glomerulonephritis.

Circulating immune complex deposition

Circulating antigen-antibody complexes are deposited in the kidney or complexes are formed locally when circulating free antigen has become trapped in the glomerulus, when they produce injury through the binding of complement system. The antigen may be exogenous e.g. bacteria (group A beta hemolytic streptococci cause glomerulonephritis) or endogenous e.g. in SLE in which antibodies against host DNA are produced. This is the most common mechanism of glomerulonephritis.

Some causes of immune complex- mediated glomerulonephritis	
Viruses • Hepatitis B and C • Epstein – Barr virus • Coxsackie virus • Varicella • HIV • Mumps • Measles	**Bacteria** • Group A beta-hemolytic streptococci • Streptococcus viridans (in endocarditis) • Staphylococci • Treponema pallidum (causing syphilis) • Gonococci • Salmonella
Parasites • Plasmodium malariae • Scistosoma • Filariasis	
Drugs • Penicillamine	**Host antigens** • DNA in SLE • Malignant tumors

Anti-GBM antibody disease

Antibodies (antiglomerular basement membrane) react with an antigen in the glomerular base membrane & produce glomerulonephritis. This mechanism is responsible for < 5% cases of glomerulonephritis. Example is Goodpasture's syndrome.

Secondary mechanisms of glomerular injury

These pathogenic mechanisms activate secondary mechanisms that produce glomerular damage such as complement activation, fibrin deposition, platelet aggregation, inflammation with inflammatory cytokines and free radical induced damage.

CLINICAL FEATURES

Glomerulonephritis presents in one of the four ways:

1. Asymptomatic proteinuria and / or microscopic hematuria – discovered on routine medical examination.
2. Acute nephritic syndrome.
3. Nephrotic syndrome: it may be pure nephrotic or mixed nephrotic/nephritic syndrome.
4. Rapidly progressive glomerulonephritis.

Correlation between the histological types of glomerulonephritis (GN) and the clinical picture

Histological type	Most common clinical presentation
Proliferative GN 1. Diffuse 2. Focal segmental 3. Rapidly progressive 4. Membranoproliferative	 1. Acute nephritic synd 2. Hematuria, proteinuria 3. Progressive renal failure 4. Acute nephritic or nephritic syndrome
Membranous GN	Nephrotic syndrome in adults
Minimal change disease	Nephrotic syndrome especially in children
IgA nephropathy	Hematuria
Focal glomerulosclerosis	Proteinuria or nephrotic syndrome

Correlation between histological pattern, clinical features and etiologies of glomerulonephritis		
Histologic pattern	Clinical presentation	Etiology
Diffuse proliferative GN	Acute nephritic synd, acute renal failure	Idiopathic, Post- streptococcus SLE, Endocarditis Henoch- Schonlein
Focal proliferative GN	Mild to moderate decreased GFR, proteinuria, hematuria	Milder form in early phase of diffuse proliferative GN
Membranoproliferative GN	Combination of nephritic and nephritic syndrome	Idiopathic, measles, hepatitis B and C
Rapidly progressive GN or Crescentic GN	Renal failure	Microscopic polyangitis Wegener's granulomatosis Goodpasture's syndrome
Minimal change GN	Nephrotic syndrome especially in children	Interstitial nephritis, HIV, Heroin Lymphoma
Membranous GN	Nephrotic syndrome	Idiopathic, Hepatitis B, C Syphilis, malaria
Focal segmental glomerulosclerosis	Nephrotic syndrome	Idiopathic. HIV, heroin

ACUTE NEPHRITIC SYNDROME

Acute nephritic syndrome indicates an inflammatory process causing renal dysfunction over days to weeks that may or may not resolve. In severe cases it may cause more than 50% loss of nephron function over the course of just weeks or months. It is characterized by the abrupt onset of:

- Hematuria with RBC casts or dysmorphic RBCs typically seen on urine microscopy.
- Proteinuria (usually non-nephrotic range).
- Renal impairment: manifesting as oliguria, uremia, raised urea and creatinine.
- Hypertension due to salt and water retention.
- Edema (usually periorbital, leg or sacral) due to salt and water retention.

ACUTE NEPHRITIC SYNDROME

- Hematuria (micro or macroscopic)
- Proteinuria
- Hypertension
- Edema
- Oliguria
- Uremia

Glomerual diseases with nephritic presentation

- Post-streptococcal glomerulonephritis (most common)
- IgA nephropathy
- Henoch – schonlein purpura
- Wagener's granulomatosis
- Goodpasteur's syndrome
- Polyarteritis nodosa
- Acute interstitial nephritis
- Essential mixed cryoglobinemia

INVESTIGATIONS

Serum chemistries

- Complement levels
- ANA, ANCA, anti- GBM antibodies, cryoglobulins
- Hepatitis C and B
- ASO titier
- C3 nephritic factor

Urinalysis

- Dysmorphic red cells
- Red cell cast
- Proteinuria

Renal biopsy

If there is no contraindication

Treatment

- Reduction of hypertension
- Salt – water restriction
- Diuretics
- Corticosteroids and cytotoxic drugs (according to the histological pattern—not effective for all cases).

The measurement of complement level is useful for the different diagnosis as following:

DIFFERENTIAL DIAGNOSIS OF NEPHRITIC SYNDROME

Low serum complement level	Normal serum complement level
Acute poststreptococcal glomerulonephritis	IgA nephropathy
Membranoproliferative glomerulonephritis	Rapidly progressive glomerulonephritis
SLE	Polyarteritis nodosa
Subacute bacterial endocarditis	Wagener's granulomatosis
Cryoglobinemia	Henoch-Schonlein purpura
	Goodpasture's syndrome
	Polyarteritis nodosa

POST-STREPTOCOCCAL GLOMERULONEPHRITIS (GN)

It results as a postinfectious complication of nephritogenic strains of group A beta-hemolytic streptococcal infection of throat or skin. Pharyngitis is a common antecedent infection; glomerulonephritis develops in less than 5% of these infected cases, usually within a 1-3 week latent period. Streptococcal skin infection leads to glomerulonephritis in about 50% of infected cases.

Post-streptococcal GN is more common in children aged 3-12 years.

The 1-3 weeks interval b/w infection and development of signs and symptoms of renal involvement reflects the time for immune complex formation and deposition and glomerular injury to occur.

Patient presents with nephritic syndrome manifesting as malaise, cola-colored urine, mild hypertension, periorbital edema and non-nephrotic range protenuria.

Investigations

- *Urinalysis*: It shows RBCs and RBC casts, WBC and proteinuria.
- *Antistreptolysin-titre:* elevated, more than 1:3000.
- *Serum complements:* C3 and C4 level is low (returns to normal at 6-12 weeks).
- *Serum urea, creatinine:* elevated.
- *Creatinine clearance*: reduced.
- *Renal biopsy:* not required in children, usually required for diagnosis in adults who develop acute nephritic syndrome.

Management

- Bed rest
- Salt free diet
- Protein restriction only if uremia occurs
- Daily record of fluid intake & output
- Daily weighing to check change in the body fluid status
- Regular measurement of blood pressure
- Diuretics: to reduce hypertension and edema
- Antihypertensive drugs may be required
- Antibiotics: if culture is positive.

Complications

- Acute renal failure
- Acute heart failure with pulmonary edema due to salt & water retention
- UTI
- Hypertensive encephalopathy

Prognosis

Prognosis in children is excellent. Oliguria improves within a week. A small number of adults who develop this disease develop hypertension and/or renal impairment later in life.

CLINICAL FEATURES OF ACUTE GN IN CHILDREN

- History: commonly a preceding infection
- Generalized edema: salt and water retention producing edema most marked around the eyes
- Breathlessness: due to pulmonary edema and in severe cases pleural effusion
- Anorexia: sometimes associated with vomiting and upper abdominal pain
- Hypertension: rarely hypertensive encephalopathy
- Fits: febrile, hypertensive or due to sodium retention
- Urinary abnormalities: oliguria, hematuria and proteinuria

IgA NEPHROPATHY

- It is a disease of IgA deposition in the glomerual mesengium. It is most commonly seen in children and young adults, male affected twice of females.
- Presentation is often an episode of gross hematuria usually associated with upper respiratory tract infection (hematuria occurs along with upper respiratory infection while in post-streptococcal glomerulonephritis renal involvement is after 1-3 weeks of infection).
- About one third show clinical remission, 40-50% will have progressive renal insufficiency while the remainder show chronic microscopic hematuria with stable serum creatinine.
- Hypertension, proteinuria and male gender are poor prognostic factors.
- Serum IgA is elevated in 50% of cases, serum complements are normal and renal biopsy is the standard for diagnosis.
- If nephritic syndrome is present give prednisolone 60mg orally daily for 4-6 weeks, it can cause remission but does not halt the progression of renal disease. Control of blood pressure is required. Fish oil 12g daily may retard the loss of renal function in mild cases. Renal transplantation is the best option for end stage renal disease.

HENOCH-SCHONLEIN PURPURA

- This is a vasculitis of unknown cause, most common in children with male predominance.
- It presents with palpable purpura, arthralgias, melena. Purpuric skin lesions are most often on lower extremities.
- Patient also has renal insufficiency with nephritic presentation. Most patients recover fully over several weeks.

WEGENER'S GRANULOMATOSIS

It is a granulomatous vasculitis of the upper and lower respiratory tract together with glomerulonephritis. Along with microscopic polyangitis and Shrug – Strauss syndrome it is included in ANCA – associated glomerulonephritis. (ANCA is antineutrophilic cytoplasmic antibodites).

In Wegner's granulomatosis there is necrotizing inflammation of glomeruli and respiratory tract (nasopharynx, lung).

Clinical features

1. *Systemic inflammatory features:* fever, malaise, weight loss.
2. *Renal features*: hematuria, proteinuria.
3. *Respiratory features:* nodular upper or lower respiratory tract lesion that can cavitate and bleed.
    - Upper respiratory features may be paranasal sinus pain and purulent or bloody nasal discharge (due to sinusitis) with or without nasal mucosal ulceration. Nasal septal perforation may follow, leading to saddle nose deformity.
    - Lower respiratory features may be cough, hemoptysis, dyspnea and chest discomfort. There may be asymptomatic pulmonary infiltrates.
4. *Eye features:* Conjunctivitis, scleritis, episcleritis in more than 50% of cases.
5. *Skin features:* Papules, vesicles, palpable purpura, ulcers or nodules in about 46% of cases.

Investigation

- Serology shows ANCA in more than 90% of cases.
- Biopsy of tissue shows necrotizing granulomatous vasculitis.
- ESR: markedly elevated.
- CP: anemia and leukocytosis.

Treatment

- Methylprednisolone 1-2 mg/kg/d for 3 days followed by prednisolone 1mg/kg/d for 1 month with a slow taper in next 6 months.
- Cyclophosphamide 2 mg/kg orally for 1 year.
- Prognosis depends on extent of renal involvement.

GOODPASTURE'S SYNDROME

Goodpasture's syndrome is defined as a clinical syndrome comprising glomerulonephritis and pulmonary hemorrhage; injury to both is mediated by anti-glomerular basement (anti-GBM) antibodies. It presents with recurrent hemoptysis and severe progressive proliferative GN.

Clinical features

Goodpasture's syndrome involves mostly young persons aged 5-40 years. It is 6 times more common in males. The onset of disease is preceded by upper respiratory tract infection in 20-60% of cases.

- Glomerulonephritis presents with hematuria, proteinuria and rapidly progressive renal failure over weeks with or without hemoptysis. Hemoptysis usually precedes nephritis by weeks or months. Hypertension is uncommon.
- Pulmonary component presents with hemoptysis and dyspnea.

Investigations

- Iron deficiency anemia, normal serum complements.
- Chest x-ray may show pulmonary infiltrates.
- Diffusion capacity of carbon monoxide is markedly increased due to uptake of carbon monoxide by alveolar blood (while it is reduced in infection or pulmonary edema).
- Diagnosis is confirmed by detecting anti-GBM antibodies present in > 90% of cases.
- Renal biopsy is gold standard for nephritis.

Treatment

- Plasma exchange therapy to remove circulating antibodies performed daily until anti- GBM antibodies are not detected in the circulation (usually 1-2 weeks)
- Prednisolon 1mg/kg/day plus cyclophophomide or azathioprin.

Prognosis

One year survival is more than 90% if treatment is started before serum creatinine exceeds 5mg/dl and 10% in advanced renal failure.

NEPHROTIC SYNDROME

The nephrotic syndrome consists of the following features:

- Heavy proteinuria (>3g/day)
- Hypoalbuminenia
- Edema
- Hyperlipidemia
- Hypercoagulability

PATHOGENESIS

Proteinuria:

Injury to the capillary wall of the glomeruli results in increased permeability to the plasma proteins, allowing protein to escape from the plasma into the glomerular filtrate, resulting in proteinuria.

Hypoalbuminaemia

Proteinuria results in decreased serum albumin resulting in hypoalbuminemia. Urinary loss of 3-5 g of protein daily is required to produce hypoalbuminemia in adults.

Generalized edema

Cause of edema is salt and water retention due to renal disease. Hypoalbuminaemia may be the contributing factor in edema formation because it results in decreased colloid osmotic pressure which in turn allows fluid to escape from vessels and to produce generalized edema.

Hyperlipidemia

Hypoalbuminemia triggers increased synthesis of all forms of plasma proteins including lipoproteins resulting in hyperlipidemia.

Hypercoagulability

It may result from:

- Increased urinary loss of antithrombin III.
- Altered levels and / or activity of protein C and protein S.
- Hyperfibrinogenemia. Due to increased hepatic synthesis.
- Impaired fibrinolysis.
- Increased tendency of platelet aggregation.

ETIOLOGY OF NEPHROTIC SYNDROME

Pure nephrotic syndrome

Primary glomerular disease

- Minimal change nephropathy
- Focal segmental glomerulosclerosis
- Membranous GN (most common cause in adults > 40 years of age).

Secondary glomerulonephritis associated with systemic disease.

- Diabetic nephropathy
- Amyloidosis
- Drugs: penicillamine, gold, mercury, cadmium
- Allergic reaction: allergy to poison ivy, pollens, bee stings and cow milk.

Mixed nephrotic / nephritic syndrome

Primary glomerular disease

- Membranoprolifterative glomerulonephritis

Secondary glomerulonephritis associated with systemic disease.

- Membranoprolifterative glomerulonephritis.
- SLE
- Henoch – Schonlein purpura
- Mixed essential cryoglobulinemia

Glomerulonephritis causing nephrotic syndrome and their associations
All these clinical disorders may be written in the causes of nephrotic syndrome
Minimal change disease Allergy, NSAIDS, Hodgkin's disease, HIV. IgA nephropathy, diabetes, heroin use
Focal & segmental GN Idiopathic (mostly), diabetes, Heroin abuse, HIV, obesity, reflux nephropathy, sickle cell nephropathy.
Membranous GN Idiopathic (mostly), **Infections:** hepatitis B and C, syphilis, malaria, leprosy, filariasis, hydatid cyst, endocarditis. **Tumors:** Hodgkin's lymphoma, carcinoma of GI, renal cell, bronchogenic, thyroid, breast, melanoma. **Autoimmune diseases:** SLE, Graves disease, primary biliary cirrhosis, myasthenia gravis, ankylosing spondylitis. **Drugs:** gold, penicillamine, captopril, NSAIDs. **Miscellaneous:** sarcoidosis, sickle cell disease, Crohn's disease, Fanconi's syndrome and Guillain- Barre syndrome
Membranoproliferative GN Upper respiratory tract infection Hepatitis B and Hepatitis C Leukemia , lymphoma, bacterial endocarditis

CLINICAL FEATURES

Edema:

- Peripheral edema involving upper limbs & mostly lower limbs. In children it may be more obvious on the face (periorbital edema) & abdomen (ascites).
- Intense edema of scrotum or vulva may occur.
- There may be bilateral hydrothorax.
- Edema of intestine causes anorexia, diarrhea and vomiting.

Malnutrition:

Malnutrition may be due to proteinuria, frequent infections & muscle wasting.

Features of underlying cause

Features of cause of nephritic syndrome may be present e.g. butterfly rash in SLE and neuropathy or retinopathy in diabetes mellitus.

Hypercoagulability

Hypercoagubility manifests as peripheral arterial or venous thrombosis, renal vein thrombosis and pulmonary embolism.

Infections:

There is an increased susceptibility to infection due to urinary loss of IgG antibodies.

INVESTIGATIONS

1. Urine D/R – proteinuria
2. 24 hours urinary proteins: usually more than 3g/day.
3. Serum albumin – less than 3g/dl and total serum protein < 6 mg/dl.
4. Low-density lipoprotein (LDL) is elevated but HDL is usually normal.
5. Raised ESR due to increased serum fibrinogen
6. Blood sugar for diabetes & antinuclear factor for SLE,
7. Hepatitis B serology, serum complements.
8. Renal biopsy: confirms diagnosis.

Renal biopsy is not indicated in the following condition

- Children under 10 years
- Known diabetic
- Patient on drugs e.g. penicillamine (only stop the drug).

COMPLICATIONS

- Protein malnutrition
- Hypercoagulability – due to rise in many clotting factors.
- Impaired resistance to infection (due to low body immunoglobulins as a result of hypoproteinaemia)
- Sepsis, blood loss and hypovolemia may lead to acute oliguric renal failure.

Differential diagnosis

Nephrotic syndrome is a common short case. It must be differentiated from cardiac failure, cirrhosis of liver and abdominal tuberculosis.

MANAGEMENT

Diet

- Low salt diet.
- Moderate protein restriction (0.5-0.6 g/kg/d) because increased protein intake may have an adverse effect on renal function in some diseases.

Diuretics

- Bendrofluazide 5 mg daily OR
- Frusemide (Lasix) 40-120 mg daily with KCl in moderate to severe edema.

Hypercholesterlemia

HMG-CoA reductase inhibitors are preferred for treatment of hypercholesterolemia such as atrovastatin.

Hypercoagulability

Patient with serum albumin less than 2g/dl can become hypercoagulable. Anticoagulation therapy is required when there is evidence of thrombosis.

Oliguric renal failure

- Maintain blood pressure & fluid volume
- Albumin infusion with mannitol may initiate a diuresis in oliguric renal failure.

Specific therapy

Minimal change disease

- Minimal change disease is the most common cause of nephrotic syndrome in children while in adults it causes nephrotic syndrome in about 20% of cases. It does not progress to renal failure.
- Prednisolone 60mg/day for 8 weeks corrects urinary protein leak in more than 95% of children. Response in adults is significantly lower and response may occur after several months of steroid therapy. Treatment should be continued for several weeks after complete remission of proteinuria. Relapse is common that requires further corticosteroid courses.
- In steroid resistant cases cyclophosphomide 3 mg/kg is given for 6-8 weeks.
- H2-blocker antagonist should always be given in steroid therapy to prevent peptic ulcer.

Membranous glomerulonephritis

- It is the most common cause of primary nephrotic syndrome in adults, usually in 5th and 6th decade and almost always after age 30.
- There is high incidence of renal vein thrombosis. Occult neoplasm of lung, stomach and colon may be found in 50 % of cases.
- About 50% patients progress to end stage renal disease in 3-10 years.
- Immunosuppressive therapy is based according to the amount of proteinuria. Prednisolone & cytotoxic drugs such as azathioprine, chlorambucil, cyclosporine or cyclophosphamide for 6 months.

Focal segmental glomerulosclerosis

- It usually presents with nephritic/nephrotic mixed picture.
- Treatment is controversial, prednisolone 1-1.5 mg/kg/d for 4-weeks followed by 1mg/kg/d every other day for 4-weeks is used in patients with frank nephrotic syndrome. Cytotoxic drugs should be given in refractory cases.

NEPHRITIC / NEPHROTIC SYNDROME

Causes are SLE and membranoprolifterative glomerulonephritis.

ACUTE RENAL FAILURE (ARF)

Acute and reversible deterioration of renal function which develops over a period of days, or rarely weeks and results in uremia is called acute renal failure.

ETIOLOGY

Renal failure may be due to pre-renal, renal or post-renal causes.

> **CAUSES OF ACUTE RENAL FAILURE**
>
> **Pre-renal ARF**
> The kidneys are inadequately perfused and the GFR greatly diminished. This may be due to :
> - Decreased cardiac output in cardiac failure.
> - Under-filling of the vascular bed due to hemorrhage, severe fluid depletion or vasodilatation resulting from sepsis.
>
> **Renal causes of ARF**
> - Diseases of the renal arterioles such as vasculitis or microangiopathic hemolytic states, rapidly progressive (crescentric) glomerulonephritis.
> - Injury to tubular cells (acute tubular necrosis) by toxins or ischaemia. Intraluminal obstruction of nephrons from precipitation of crystals or protein.
> - Acute intestinal nephritis due to infections or drug reactions.
>
> **Postrenal causes of ARF**
> ARF is caused by obstruction of the urinary tract at any point in its course.

PRE-RENAL ACUTE RENAL FAILURE

This is also called pre- renal azotemia. About 70% cases of acute renal failure (ARF) are due to pre-renal cause. Pre-renal ARF results from hypoperfusion of kidneys due to decrease in effective arterial blood volume.It can immediately be reversed with restoration of renal blood flow, renal parenchymal damage does not occur. If hypoperfusion persists ischemia can result causing intrinsic renal failure.

COMMON CAUSES

Volume deficit:

- Hemorrhage due to trauma, GI bleed, surgery
- GI loss: vomiting, diarrhoea
- Renal loss: diuresis
- Skin loss: Sweating

Cardiovascular failure:
Cardiogenic shock

Decreased systemic vascular resistance:
Sepsis

Intravascular hemolysis
Severe liver failure (hepato-renal syndrome)

> **CAUSES OF PRERENAL ACUTE RENAL FAILURE**
>
> **Reduced circulation blood volume**
> - Hemorrhages from any cause including complications of pregnancy.
> - Trauma
> - Gastrointestinal bleeding
> - Loss of plasma as in burns and crushing injuries.
>
> **Sodium and water depletion:**
> - From the gastrointestinal tract in severe vomiting, diarrhoea, acute intestinal obstruction, paralytic ileus, pancreatitis, fistulae.
> - In urine due to excessive treatment with diuretics, diabetic ketoacidosis
> - From the skin due to sweating
>
> **Reduction of cardiac output and myocardial failure**
> - Cardiogenic shock
>
> **Peripheral vasodilatation**
> - Septicaemia
>
> **Intravascular haemolysis**
>
> **Rhabdomyolysis**
> Breakdown of skeletal muscle due to the toxic effects on the kidney of released globins.
>
> **Diseases of the major renal vessels**
> The diseases which result in renal under perfusion e.g. thrombosis of the aorta or renal arteries, or aortic aneurvsm.

CLINICAL FEATURES

1. Cause is usually obvious
2. Hypotension and signs of inadequate peripheral perfusion
3. Decreased urinary output

DIAGNOSIS OF PRE-RENAL ARF

- A complete history
- The clinical findings
- A progressive increase in blood urea and plasma creatinine.
- Serum BUN: creatinine ratio >20:1
- Urine sodium < 20 meq/L
- Urine osmolality >500 mosm/kg

Urinary indices for the diagnosis of pre-renal and renal ARF

	Prerenal	Renal cause
Urine osmolality mOsm/L	≥ 500	≤ 350
Urine/plasma creatinine ratio	≥ 40	≤ 20
BUN/plasma creatinine ratio	> 20	< 20
Fractional excretion of sodium	< 1%	>1%

MANAGEMENT

- Identify the cause and correct it
- If hypovolemia or septicaemia – restore circulation by replacing blood, plasma or saline as indicated.
- Maintain serum electrolytes; especially consider serum potassium level.
- Avoid nephrotoxic drugs.

PROGNOSIS

- Renal function in prerenal failure returns to normal completely once normal renal perfusion has been restored in early stage.
- If oliguria persists in spite of restoration of the circulation to normal then acute tubular necrosis is likely to have developed.

ARF DUE TO INTRINSIC RENAL DISEASES

Acute renal failure due to intrinsic renal disease that may result from:

- Acute tubular necrosis (ATN) that may be ischemic or nephrotoxic.
- Acute glomerulonephritis
- Acute interstitial nephritis.
- Vascular causes

ACUTE TUBULAR NECROSIS (ATN)

This is the most common cause of renal failure. And is characterized by acute tubular cell damage. Tubular cells have the capacity to regenerate and therefore returns to near normal if the patient can be kept alive during regeneration phase.

Types of Acute tubular necrosis (ATN)

Ischemic type

The pattern of acute renal necrosis is caused by prolonged ischemia due to hypoperfusion (causes are same as of pre-renal failure).

Nephrotoxic type

This type of acute tubular necrosis is caused by a variety of poisons such as:

- Drugs e.g. aminoglycosides, heavy metals
- Endogenous toxins e.g. calcium, uric acid, hemoglobin, myoglobin
- Exogenous toxins e.g. antibiotics, contrast dye.

RENAL CAUSES OF RENAL FAILURE

Intrinsic diseases of the kidney can cause acute renal failure. These disease are divided into glomerular, tubulo-interstitial or vascular disease.

Glomerular

1. Primary Glomerulonephritis
2. Secondary Glomerulonephritis
    - Diabetic nephropathy
    - Amyloidosis
    - Systemic vasculitis: SLE, Polyarteritis, Wegener's granulomatosis

Acute tubular necrosis

Ischemic

It results from hypotension

Nephrotoxic

Exogenous toxins

- Antibiotics such as aminoglycosides
- Contrast agents
- Heavy metals such as mercury
- Chemical such as carbon tetrachloride

Endogenous toxins

- Hemoglobinuria, myoglobinuria
- Multiple myeloma
- Urice acid (gout)

Acute interstitial nephritis

Usually drug induced

Vascular

- Hypertensive nephrosclerosis
- Polyarteritis nodosa
- Atheroma kidney

Functional

- ACE inhibitors, NSAIDs

CLINICAL COURSE

The clinical course of acute renal failure is relatively short lasting approximately 10-25 days during which time the individual progresses through three phases of the pathophysiological process

1. Pre-oliguric phase (0-2 days)
2. Oliguric phase (8-14 days)
3. Diuretic phase (about 10 days)
4. Recovery phase (4-6 months)

Pre-oliguric phase

- It is the period from occurrence of the precipitating event until the beginning of the oliguria.
- Symptoms of primary cause are dominant.
- Ratio of urea in urine to that in the plasma becomes low 14:1 (normal ratio is 20:1)
- Rapid reversibility if circulation is restored early and completely.

Oliguric phase

- This period is characterized by oliguria (urine volume less than 400 ml in 24 hours). Complete anuria (less than 50ml) is rare and if present the patient should be assessed for urinary obstruction.
- The longer the patient remains in this phase the poorer the prognosis due to development of complications due to excessive body fluids, electrolyte imbalance and retention of metabolic waste products.

Diuretic phase

This phase is characterized by increase in urinary output to about 3-5 liters daily and this may progress to polyuria and dehydration. Diuresis develops because damaged tubular epithelium is replaced by an epithelium which has not yet developed concentrating activity.

Recovery phase

This is the period from the stabilization of serum laboratory values until the patient attains either totally normal or optimal renal function.

DIAGNOSIS OF ACUTE RENAL FAILURE

Diagnosis of ARF due to pre-renal cause

- History and clinical examination reveals fluid loss.
- With pure prerenal failure, urine output should increase with volume replacement.
- Blood transfusion in hemorrhagic shock or normal saline if depletion is due to vomiting diarrhea or polyuria.

Diagnosis of ARF due to renal cause

- Early renal damage due to acute tubular necrosis (ATN) may be reversible (incipient ATN) if the kidneys are subjected powerful diuretic stimulus such as diuretic combination of 20% mannitol 100ml I/V over 5-10 min followed by frusemide 120mg (Lasix) I/V over 5-10 minutes.
- A satisfactory response is b/w 10-40 ml/hour, the diuretic stimulus may be repeated once after 2 hour.
- If thee is no increase in urine output, this procedure should not be repeated a third time.

If these measures do not induce diuresis, the diagnosis of pre-renal azotemia or incipient ATN has been excluded. The differential diagnosis then lies b/w intrinsic renal disease & obstructive nephropathy.

<u>Dopamine infusion in ATN</u>

Infusion of dopamine in low dosage causes renal vasodilatation and a sodium diuresis, it also increases cardiac output by its positive inotropic effect. In large doses, dopamine casuses vasoconstriction. It may be combined with large doses of frusemide.

Distinction b/w ARF due to Renal & Post Renal cause

- Urine analysis: hemature with red-cell casts, recent trauma or sepsis with hypertension and exposure to nephrotoxic drugs all suggest intrinsic disease (i.e. renal cause)
- Previous history of stone disease suggests obstructive nephropathy. Anuria should always be considered due to obstruction until proved otherwise.

Difference between acute and chronic renal failure		
Feature	**ARF**	**CRF**
History	Normal renal function	History of elevated urea and creatinine
Kidney size	Normal	Small except in: Diabetes Multiple myeloma, hydronephrosis, polycystic kidney, amyloidosis
Bone film	No evidence of renal osteodystrophy	May show renal osteodystrophy
CBC	Anemia may be present	Anemia frequently present

INVESTIGATIONS

- Serum urea, creatinine
- Serum electrolytes: hyperkalemia is common.
- Serum calcium and phosphate
- Urine analysis, urinary electrolytes
- CBC: to look for anemia
- Ultrasound kidney: it shows renal size that helps in differentiation between acute and chronic renal failure, it also helps in identification of obstruction.

MANAGEMENT

EMERGENCY RESUSCITATIVE MEASURES

1. Hyperkalaemia: must be corrected to prevent cardiac arrhythmias. It can be reduced rapidly by Inj. 50CC of 50% Dextrose water + 10 units plain insulin
2. Acidosis: is corrected with sodium bicarbonate I/V and dialysis.
3. Hypovolemia is corrected with blood transfusion or appropriate fluids.
4. Pulmonary edema: if patient comes with pulmonary edema, then hemodialysis or peritoneal dialysis is required.

MANAGEMENT OF OLIGURIC PHASE

1. Maintenance of fluid balance
2. Maintenance of electrolyte balance
3. Control of uremia
4. Control of acidosis
5. Maintenance of nutrition
6. Management of hypertension (however hypertension is uncommon)

Maintenance of fluid balance

- Daily fluid intake should be equal to the volume of the urine output + 400ml (for insensible loss of water).
- If patient presents with fluid overload (i.e. raised JVP with systemic or pulmonary edema) fluid should be removed & large doses of frusemide 180mg I/V should be given. Once the fluid balance has been corrected, it must be maintained with urine output plus 400 ml for insensible loss.

Maintenance of electrolyte balance

In oliguric phase kidney cannot excrete sodium or potassium. Therefore intake of both must be reduced. Hyperkalemia if occurs, should be treated rapidly with dialysis.

Control of uremia

In acute renal failure tissue metabolism is greatly increased and the accumulation of waste products is faster, therefore dietary restriction of protein should be advised with adequate calories from carbohydrate and fat.

Control of acidosis

Acidosis in oliguric phase can only be corrected by dialysis. Sodium bicarbonate may cause fluid overload.

Other measures

1. Nausea, vomiting: Metochlopramide (Maxolon) 10mg I/M.
2. For sedation & to prevent fits – Diazepam
3. Anemia – packed cell volume
4. To prevent stress ulcer – Rantidine (Inj. Zantac 50mg) twice daily.

Indications of dialysis in ARF

1. Severe hyperkalaemia (K > 7 mmol/L
2. Severe or worsening metabolic acidosis (pH < 7.2)
3. Fluid overload not controlled by conservative measures causing pulmonary edema
4. Uremic encephalopathy (seizures)
5. Uremic pericarditis
6. Blood urea above 200 mg/dl
7. Creatinine above 10 mg/dl

Dialysis may be peritoneal or hemodyalisis

MANAGEMENT OF DIURETIC PHASE

After about 10-20 days renal functions return but in a number of patients urinary output becomes very high 3-5 litres/day because damaged tubules has not fully recovered their ability to retain salts and water.

This phase remains for 3-4 days. Sufficient fluid and electrolytes must be given for replacement.

ARF DUE TO POST RENAL CAUSE

- History of previous urinary symptoms may be present, such as loin pain, hematuria, renal colic, nocturia or difficulty in mictrution.
- In contrast to oliguric (as in renal type ARF) anuria is common.
- Antegrade or retrograde pyelography or cystoscopy may reveal obstruction

Management

Relieve obstruction

COMPLICATIONS OF ACUTE RENAL FAILURE

1. Fluid overload
2. Hyponatremia
3. Hyperkalemia
4. Infections
5. Metabolic acidosis
6. Malnutrition
7. Anemia
8. Bleeding disorders
9. Cardiac arrhythmias
10. Gastrointestinal bleeding
11. Uremic syndrome

MANAGEMENT OF COMPLICATIONS OF ACUTE RENAL FAILURE

In established acute renal failure (oliguric phase) following complications are common and they should be managed properly.

Fluid overload

This manifests as nausea, headache, lethargy, elevated JVP, pulmonary and dependent edema, ascites and pleural and pericardial effusion. Hypertension is also caused by fluid overload.

Management

- Salt and water restrictions.
- Diuretics
- Dialysis (if above measures fail)

Hyponatraemia

This is dilutional hyponatremia due to excessive intravascular fluid resulting from inappropriate amounts of IV fluids such as 5% decrease or if the patient continues to drink freely despite oliguria.

Management

- Restriction of oral water intake
- Restriction of hypotonic IV solutions

Hyperkalemia

It results from impaired excretion of potassium which comes from diet, potassium containing fluids and potassium released from injured tubular cells.hyperkalemia may lead to ventricular fibrillation. ECG changes of hyperkalemia are tall T wave, flat P wave, increased PR interval, widening of QRS complex and VF in sequence.

Management

Mild hyperkalaemia: restriction of dietary K+ intake and K+ binding ion-exchange resin.

Severe hyperkalaemia (K+ over 6.5) – requires emergency treatment with:

1. *Calcium gluconate* (to prevent arrhythmias due to hyperkalemia). 10 ml of 10% solution given IV over 2-3 min. It is only cardioprotective and does not change serum potassium level.

- *Glucose and insulin* (50cc of 50% dextrose water + 10 units of plain insulin I/V over 10 min). Insulin causes shift of K inside the cell. If effective, the plasma K level falls 0.5-1.5 mmol/L in 15-30 min and the effect lasts for several hours.

- *Bicarbonate:* 1-2 ampules IV also shifts K inside the cell.
- *Beta 2-agonist:* salbutanol (Ventolin 10-20mg in 4 ml saline) through nebulization promotes cellular uptake of K. Onset of action is within 30min, lower plasma K by 0.5-1.5 mmol/lit and the effect lasts for 2-4 hours.
- *Cation exchange resins* such as kayexalate 25-50g mixed with 100ml of 20% sorbitol. It will act within 1-2 hours and effect lasts for 4-6 hours.
- *Dialysis:* life-threatening complications not responding to medical treatment.

Infections

Patients with ARF are predisposed to infections. It is number one cause of death in ARF patients. Identification of source and suitable antibiotics are required.

Metabolic acidosis

Metabolism of dietary protein yields 50-100 mmol per day of fixed non-volatile acids, which must be excreted by the kidneys to preserve acid-base homeostasis. Due to renal failure this acid accumulate in the body resulting in metabolic acidosis.

Management

- Restriction of dietary protein
- Sodium bicarbonate to maintain serum bicarbonate above 20 meq/L
- Dialysis

Malnutrition

Malnutrition is one of the most troublesome complications of ARF. It is caused by a number of factors such as increased breakdown and reduced synthesis of muscle protein, anorexia and increased hepatic gluconeogenesis.

Management

- Provide adequate calories to prevent catabolism.
- Most of the calories are provided in the form of carbohydrate. Protein should be given in small quantity (0.6-0.8 g/day)

Hematological dirorders

- Anemia: due to hemodiluation, inhibition of erythropoiesis, hemolysis, bleeding, reduced RBC survival time and frequent phlebotomy. It may require blood transfusion.
- Bleeding disorders: due to platelet dysfunction and clotting factors abnormalities.

Management

Transfusion, estrogen, cryoprecipitate, dialysis.

Cardiac disorders

Arrhythmias, MI and pulmonary embolism.

Gastrointestinal disorders

GI bleeding

Uremic syndrome

- It is manifested as anorexia, nausea, vomiting ileus, pericarditis, pericardial effusion, lethargy, confusion, stupor, coma, agitation, psychosis and seizures.
- Urea and other toxic compounds are thought to be involved in other development of uremic syndrome.
- Onset of uremic syndrome needs emergency dialysis.

Other disorders

- Hyperphosphataemia should be managed with aluminium containing antacids.
- Hypocalcaemia – although serum calcium is low it does not require specific treatment.

INTERSTITIAL NEPHRITIS

ACUTE INTERSTITIAL NEPHRITIS

Acute interstitial nephritis accounts for 10-15% of cases of intrinsic renal failure (ARF due to intrinsic renal disease). Drugs are precipitating factor in more than 70% of cases. However toxins, some systemic diseases and infections may also involved. It may be idiopathic.

ETIOLOGY

Drugs

- Penicillins
- Cephalosporins
- Sulfonamides
- Rifampicin
- Phenytoin
- NSAIDs
- Allopurinol
- Frusemide

Systemic disease

- SLE
- Sarcoidosis
- Sjogren's syndrome
- Multiple myeloma
- Cryoglobinemia

Infections

- Leptospirosis
- Streptococcal infection
- Tuberculosis
- Pyelonephritis
- Cytomegalovirus

Clinical features

Fever, rash, arthralgia
Acute renal failure

Diagnosis

- Drug hypersensitivity reaction such as fever, rash, eosinphilia .
- Urine analysis shows RBCs, WBCs, WBC cast, proteinuria and eosinophiluria.
- Non-oliguric acute renal failure should always be investigated for acute interstitial nephritis.

Management

- Supportive treatment of ARF including hemodialysis.
- If renal failure persists after removal of precipitating factors then short course high dose steroids (methylprednisolone or prednisolone) may be given.
- Rarely leads to end –stage renal disease.

CHRONIC INTERSTITIAL NEPHRITIS

Classification of chronic interstitial nephritis

Type of disease	Examples
Chronic glomerular disease	Varying degrees of interstitial nephritis may be found in association with almost any type of glomerulonephritis.
Immune/ Inflammatory diseases	Sarcoidosis, Sjogren's syndrome, SLE, primary autoimmune tubulo-interstitial nephritis, chronic transplant rejection, amyloidosis
Tumours	Myeloma
Drugs	All drugs causing AIN, especially NSAIDs and compound analgesics (analgesic nephropathy)
Metabolic / congenital	Wilson's disease, hypokalemia, medullary sponge kidney, Hypercalcuria, hyperoxaluria, sickle-cell nephropathy
Toxins	Mushrooms, lead, Chinese herbs, Balkan nephropathy

Clinical features

Most patients present in adult life with CRF, hypertension and small kidneys.

Management

Management of CRF

PAPILLARY NECROSIS

Papillary necrosis results from infection of renal pyramids that is associated with vascular disease of the kidney or urinary tract obstruction. It is usually bilateral.

Predisposing factors

- Diabetes
- Sickle cell disease
- Chronic alcoholism
- Chronic urinary tract obstruction

Clinical features

- Fever, chills
- Hematuria
- Pain in flank or abdomen due to obstruction of ureter by necrotic tissue.
- Acute renal failure with oliguria or anuria
- Asymptomatic sloughing of pyramid with chronic urinary infection detected when necrotic tissue is passed in urine.

Diagnosis

- Necrotic tissue in urine.
- *Ring shadow* on IVP representing radiolucent sloughed papilla surrounded by the radiodense contrast material in calyx.
- If renal function deteriorates suddenly in diabetic patient or with chronic urinary obstruction, the diagnosis of papillary necrosis should be considered even in the absence of fever and pain.

Treatment

Supportive measures

Treatment of underlying cause and precipitating factors.

ANALGESIC NEPHROPATHY

Chronic use of high dose of analgesic may lead to decline in renal function due to chronic papillary necrosis and chronic diffuse tubulointerstitial damage to the renal cortex.

Details of papillary necrosis is given above and tubulointerstitial nephritis in next the pages.

- Patients with analgesic nephropathy are unable to produce maximally *concentrated urine* due to underlying medullary and papillary damage.
- Distal tubular acidosis (associated with analgesic nephropathy) contributes to the development of *nephrocalcinosis.*
- Anemia is more severe as compared to level of renal insufficiency.
- Kidneys become shrunken and calyces are deformed producing "ring sign" on IVP pathognomonic of papillary necrosis.
- Transitional cell carcinoma may develop in the urinary pelvis or ureters as a late complication of analgesic abuse.

Treatment

- Discontinuation of analgesics may improve the renalfunction with time.
- Supportive measures in renal impairment.

DRUG-INDUCED IMPAIRMENT OF RENAL FUNCTION

Pre-renal

Impaired perfusion of the kidney can result from drugs that cause:

- Hypovolemia: due to:
  - Frusemide (Lasix) esp. in elderly patients.
  - Hypercalcemia causing renal salt and water loss.
- Decreased cardiac output which impairs renal perfusion e.g. due to beta blockers
- Decreased renal blood flow e.g. due to ACE inhibitors.

Renal

1. *Acute tubular necrosis* produced by direct nephrotoxicity e.g. prolonged or excessive use of:
   - Aminoglycosides (streptomycin, gentamicin, kanamycin)
   - Amphotericin B
   - Cephaloridine
   - Heavy metals
   - Carbon tetrachloride
   - (Combination of aminoglycoside or cephaloridine with frusemide is particularly nephrotoxic).

2. *Acute tubulointerstitial nephritis* (cell mediated hypersensitivity nephritis) produced by:
    - Sulphonamides
    - NSAIDS
    - Penicillins

3. *Chronic tubulointerstitial nephritis*

4. *Immune complex-mediated glomerulonephritis* produced by :
    - Penicillamine

Post-renal

Retroperitoneal fibrosis with urinary tract obstruction may result from methylsergide

USE OF DRUGS WITH IMPAIRED RENAL FUNCTION

- No drug should be given unless specifically indicated.
- The least toxic alternative must be chosen
- Determine recommended dose for degree of renal impairment (use creatinine clearance as indication of degree of impairment). Adverse effects of drug should also be known.
- The patient must be observed regularly for signed of adverse effects and the drug stopped or the dose reduced if these develop.
- Measurement of plasma drug concentration may be helpful in monitoring dosing schedule.
- If a drug is more than 50% eliminated unchanged by the kidneys or has active metabolites that are eliminated by the kidneys, the maintenance dosage must be altered in renal insufficiency. Creatinine clearance can be used as a guide to reducing maintenance dosages.

DRUGS THAT SHOULD BE AVOIDED IN SEVERE RENAL INSUFFICIENCY

- Chloroquine
- Chloramphenicol
- Lithium
- Metformin
- Methotrexate
- Mesalazine
- NSAIDs
- Sulphonylurea
- Tetracycline

DRUGS WHOSE DOSE SHOULD BE REDUCED IN RENAL IMPAIRMENT

- ACE inhibitors
- Aminoglycosides
- Chlorpropamide
- Digoxin
- Atenolol
- Azathioprine
- Cephalosporin isoniazid
- Cimitidine
- Penicillins
- Sulphonylurea

RENAL INVOLVEMENT IN SYSTEMIC DISEASES

- SLE (Lupus nephritis)
- Systemic vasculitis
    - Polyarteritis nodosa
    - Microscopic polyangitis
    - Wegener's granulomatosis
- Cryoglobinemia
- Diabetes mellitus
- Systemic sclerosis
- Amyloidosis
- Hemolytic uremic syndrome
- Thrombotic thrombocytopenic purpura
- Multiple myeloma
- Contrast nephropathy
- Sickle cell disease
- Tuberculosis
- Gout

CHRONIC RENAL FAILURE (CRF)

progressively worsening

Chronic renal failure is the irreversible deterioration in renal function which results from a diminished mass of the excretory, metabolic and endocrine functions of the kidney which leads to the development of the clinical syndrome of uremia.

CRF is a slowly progressive, irreversible cessation of renal function manifesting as biochemical, metabolic, fluid, electrolyte, and acid-base imbalances. Often a gradual decline in GFR occurs over a period of years, however for diagnosis of chronic renal failure GFR must be reduced for at least 3-6 months.

- CRF is given in more detail for the physicians while the medical students can skip the details of management.

Normal kidney functions

- *Excretory.* Excretion of waste product & drugs.
- *Regulatory* control of body fluid volume and composition (acid-base balance)
- *Endocrine* production of erythropoietin, rennin and prostaglandin
- *Metabolic* activation of vit D.

STAGES OF CRF

There are 4 stages of functional deterioration in renal failure.

1. **Diminished renal reserve**

- There is mild reduction in renal function.
- Creatinine clearance decreases from normal 120 ml/min to approximately 50 ml/min.
- Increase in serum creatinine level from a normal range of 0.7 – 1.5 mg/dl to a range of 1.6-2.0 mg/dl.
- Renal regulatory, excretory and metabolic functions remain intact and the patient is symptom free.

2. **Renal insufficiency**

- Creatinine clearance continues to decrease to about 10 ml/min.
- Serum creatinine rises to the range of 2.1-5.0 mg/dl.
- Initial manifestations of renal insufficiency usually appear.
- Further stress due to infection or dehydration intensifies the symptoms requiring therapeutic intervention.

3. **Renal failure**

- Creatinine clearance has decreased to about 5 ml/min
- Serum creatinine is greater than 8 mg/dl.
- Patient is symptomatic and requires medical management.

4. **Uremic syndrome**

- Creatinine clearance is < 5 ml/min.
- Serum creatinine is > 12 mg/dl.
- Patient develops clinical manifestations in every system of the body.

INCIDENCE OF CAUSES OF CRF

Disease	%
Diabetes Type I Type II	37 15 22
Hypertension (includes renal artery stenosis)	29
Glomerulonephritis	11
Tubulointerstitial disease (includes obstruction)	4.5
Cystic / Hereditary / Congenital diseases	3.5
Secondary glomerulonephritis	2.4
Neoplasms (include multiple myeloma)	1.6
Miscellaneous / unknown	5-10
Chronic pyelonephritis is a common cause of CRF in Pakistan	Data not available

CAUSES OF CHRONIC RENAL FAILURE

PRE-RENAL

- Hypertensive nephrosclerosis
- Renal artery stenosis

RENAL

Glomerular

Primary glomerular diseases

- Focal segmental glomerulosclerosis
- Membranoproliferative GN
- IgA nephropathy
- Membranous GN

Secondary glomerular diseases

- Diabetes nephropathy
- Amyloidosis
- Post-infectious GN
- Heroin nephropathy
- Collagen vascular disease
  - SLE
  - Polyarteritis nodosa

Tubulointerstitial

- Analgesic nephropathy
- Nephrotoxins e.g. heavy metals
- Multiple myeloma
- Reflux nephropathy
- Chronic pyelonephritis
- Tuberculosis

Hereditary

- Polycystic kidney disease
- Medullary cystic disease

POST-RENAL (Obstructive)

- Renal stones
- Urethral tuberculosis
- Prostatic obstruction
- Congenital defects

PATHOPHYSIOLOGY

Hyperfiltration

Reduction in renal mass leads to hypertrophy of the remaining nephrons due to adaptive hyperfiltration. This adaptation places a burden on the remaining nephrons that leads to progressive glomerular sclerosis and interstitial fibrosis.

Uremic toxins

Uremic toxins produce signs and symptoms in CRF

- By-products of protein and amino acid metabolism such as urea, creatinine etc.
- Elevated parathyroid hormone causes increased cellular calcium level in several tissues and organs especially involves in cardiomyopathy and metastatic calcification.

EFFECTS OF UREMIA ON THE BODY

Carbohydrate metabolism

- *Glucose intolerance*: due to impaired ability to metabolize glucose as a result of peripheral resistance to the action of insulin, called azotemic psudodiabetes. Severe hyperglycemia is not seen therefore no specific therapy is required.
- Because insulin is removed from plasma by renal cells which degrade it intracellularly, circulating insulin levels in plasma are slightly to moderately increased in most fasting uremic patients and sugar level may become normal in previously hyperglycemic patient. Patients have false impression that their diabetes is cured; unfortunately now they are developing renal impairment as a complication of diabetes.

Protein metabolism

- Increased catabolism of protein.
- Reduced capacity to eliminate nitrogenous end products of protein catabolism that leads to retention of nitrogenous substances. It is the major cause of organ dysfunction resulting in development of signs and symptoms of uremia.

Lipid metabolism

- Hypertriglyceridemia – due to increased insulin lipogenic effect and reduced lipoprotein lipase enzyme preventing lipid utilization.
- Low HDL
- Normal cholesterol

Fluid and electrolytes

Sodium retention due to impaired sodium-potassium pump leads to increased intracellular sodium and water causing volume overload, hypertension and edema formation.

Hypothermia

It results from retention of some toxins and impaired sodium-potassium pump

COMPLICATIONS OF RETAINED PRODUCTS

Retained products	Effects
Urea	Nausea, vomiting, fatigue, headache
Guanidine compounds	It inhibits alpha-hydroxylase activity within the kidney that leads to deficient activated vitamin D resulting in secondary hyperparathyroidism.
Beta 2 microglobulins	Neuropathy, carpal tunnel syndrome, amyloid infiltration in joints.
Parathyroid hormone (PTH)	Cardiomyopathy, metastatic calcification, osteodystrophy
Phosphate	Hypocalcemia due to deposition of calcium phosphate in the bone which is sensed by specific receptors on parathyroid gland causing hyperplasia of gland and increased secretion of PTH.
Potassium	Arrhythmias
Sodium	Hypertension, edema
Acid	Metabolic acidosis

COMPLICATIONS DUE TO DEFICIENCIES

Deficiencies	Effects
Calcium	Hypocalcemia, stimulation of PTH→osteodystrophy
Activated vitamin D	Decreased absorption of calcium from gut, stimulation of parathyroid
Erythropoietin	Anemia

CLINICAL FEATURES

- Non-specific features: nausea, vomiting, malaise, pruritus→drowsiness, diarrhea, fits and coma.
- Features of complications: anemia, bone pain etc.
- Urinary symptoms: patient may present with anuria (<50ml), oliguria (<400ml), nocturia or polyuria.

<u>*Asymptomatic:*</u> In the early stages of disease patient may be asymptomatic and renal insufficiency is revealed by discovery of proteinuria, anemia, hypertension or raised blood urea during routine examination.

<u>*Symptomatic:*</u> Symptomatic uremia mostly presents with anorexia, nausea & vomiting but it may present with symptoms of anemia, bone disease, hypertension, hypertensive heart disease, endocrine disturbances (amenorrhoea & erectile impotence)

ACUTE ON CHRONIC RENAL FAILURE

Although, as a rule, chronic renal failure is irreversible and slowly progressive, it is critical that the physician must be able to exclude the possibility of potentially reversible factors (to rule out "acute on chronic" renal failure) and to be sure that treatable causes of chronic renal failure are identified, disorders that if treated might allow for some return of renal function.

Reversible factors	Treatable factors
• Hypovolemia • Congestive heart failure • Pericardial tamponade • Severe hypertension • Catabolic state / protein loads • Nephrotoxic agents e.g. diuretics, NSAIDs • Obstructive disease • Reflux disease	• Renal artery stenosis • Malignant hypertension • Acute interstitial nephritis • Hypercalcemic nephropathy • Multiple myeloma • Obstructive nephropathy • Vasculitis • SLE • Wegener's granulomatosis • Polyarteritis nodosa

FEATURES SUGGESTING CRF RATHER THAN ARF

1. *Evidence of* **osteodystrophy** *on bone film:* X-ray changes of secondary hyperparathyroidsm do not appear unless PTH levels have been elevated for at least one year, manifesting as subperiosteal erosions along the radial side of terminal phalanges and lateral end of the clavicle.
2. **Peripheral neuropathy** (sensorimotor)
3. **Small kidneys** on ultrasound with some exceptions such as:
   CRF with normal kidney size
   - Multiple myeloma
   - Diabetic nephropathy
   - Amyloidosis
   - Polycystic kidney disease
   - Hydronephrosis
4. Prolonged uremic symptoms (long history)
5. Previous record of elevated urea, creatinine, previous history of dialysis or renal biopsy.
6. BUN, creatinine – stable in CRF while in ARF BUN raises 20-40 mg/day and creatinine 2-4 mg/day.
7. Board waxy cast on urine microscopy.

Following features may be present in acute renal failure as early as 10 days after onset, but in the presence of above features suggest CRF.

Features	ARF	CRF
Anemia	May be present	Usually present
Serum BUN & creatinine	BUN increases 20-40 mg/d And creatinine 2-4 mg/d	Stable
Serum potassium	High particularly in oliguric phase	Normal until end stage
Serum phosphorous	High	Significantly high when serum creatinine is > 3 mg/dl
Serum calcium	Low	Low
Urinary volume	Oliguric or nonoliguric	1000ml daily until end stage

EXAMINATION OF UREMIC PATIENT

GENERAL APPERANCE

- **Mental status**-conscious, drowsy, comatose.
- **Hyperventilation** – indicates metabolic acidosis
- **Hiccups**
- **Complexion** – sallow complexion due to impaired excretion of urinary pigments (urochromes) combined with anemia.
- **State of hydration**: dehydration or edema.
- In terminal ill patient: drowsiness, coma, twitching due to myoclonic jerks and epileptic seizures.

HANDS

- **Half-and-half nails** (Tarry's nail): brown line of at least 1mm wide at distal end of nail, present in 1/3 of CRF patients.
- **Anemia** – pallor palmer creases
- **Flapping tremors**
- Look for A/V fistula for dialysis.

ARMS

- **Bruising:** resulting from nitrogen retention that causes impaired prothrombin consumption, defects in platelet factor and abnormal platelet aggregation.
- **Scratch marks**: due to pruritus as a result of deposition of calcium or phosphate in the skin or stimulation of nerve endings due to some retained toxin.
- **Uremic frost**: fine white powder present on the skin due to precipitation of high concentration of urea in sweat.

FACE

- **Anemia**
- **Uremic fetor** – smell from mouth due to breakdown of urea to ammonia.
- **Mucosal ulcers**: due to dryness as a result of decreased saliva, thrush.

CHEST

- Auscultate heart for pericardial rub
- Auscultate lungs for pulmonary edema, pneumonia as the patient is prone to have infection due to immunosuppression.

ABDOMEN

- Palpate kidney for enlargement, mass, polycystic kidney.
- Auscultate renal bruit.

BACK

- Strike vertebral column with base of fist gently to elicit tenderness due to osteodystrophy.
- Renal punch: to elicit tenderness in renal angle as a manifestation of renal infection.
- Examine for sacral edema

LEGS

- Examine for edema, scratch marks
- Neuropathy manifesting as loss of sensation and absent reflexes.

FUNDI

Look for retinal changes of diabetes and hypertension.

INVESTIGATIONS IN CRF

Blood Urea:

- Urea is raised in CRF and is helpful in assessing the renal function.
- It is synthesized mainly in the liver and is the end product of protein catabolism. About 30-70% urea is reabsorbed after filtration. Dehydration causes increased urea absorption and the GFR is underestimated.

Serum creatinine:

- Creatinine is the most useful clinical test in assessing progression of renal failure. However at least 50% of renal function is lost before serum creatinine begins to rise. Therefore normal level of creatinine does not rule out impairment of renal function.
- Serial estimation of serum creatinine provides the best indication of state of renal function in patient with CRF.
- Creatinine is the product of muscle metabolism. It is freely filtered and not reabsorbed, however small amount is eliminated by tubular secretion that increases with dehydration overestimating the GFR.

Electrolytes:

- Hyponatremia is common
- Potassium is normal until end-stage.
- Calcium is low and phosphate high

Creatinine clearance:
It measures the GFR as following:

$$C = \frac{U \text{ (urinary creatinine mg/dl)} \times V \text{ (urine flow rate ml/min)}}{P \text{ (plasma creatinine mg/dl)}}$$

Normal creatinine clearance is 90-140 ml/min in men and 80-120 ml/min in women.

Ultrasound kidneys
It is useful in detecting:

- Renal size; kidneys less than 10 cm are considered small.
- Hydronephrosis
- Renal mass
- Polycystic kidney

Radionuclide studies

^{99m}Tc-DTPA

- It is used to assess GFR when urine collection is difficult or expected inaccurate.
- Helpful in the diagnosis of renal artery stenosis.
- Localizes the site of obstruction.

^{99m}Tc-DMSA

- It determines the contribution of each kidney to overall renal function.
- It localizes infection such as renal abscess or infection within a renal cyst.

Renal biopsy
Renal biopsy is indicated when there is unexplained renal failure with normal sized kidneys.

Urine analysis
Proteinuria, hematuria, broad cast

MANAGEMENT

- Dietary modifications
- Treatment of complications
- Dialysis
- Renal transplantation

DIET

Protein restriction
Early protein restriction slows the progression to the end-stage renal disease. Daily protein intake should be 0.6-1 g/kg. Protein intake should be increased during dialysis.

Potassium restriction
Required when GFR falls below 10-20 ml/min. Intake less than 60 mEq/d is recommended. Advise the patient to avoid high potassium foods (e.g. bananas, coffee, tomatoes etc.)

Phosphorous restriction
Phosphorous level should be kept below 4.5 mg/dl. Avoid phosphorous rich food such as eggs, dairy products and meat.

Carbohydrate & fat should be adequate to provide energy to the body.

Salt and water restriction

- Patient of CRF should be volume expanded as suggested by small amount of pedal edema. Patient should take 2-3 L/d to excrete waste products as effectively as possible by remaining intact nephrons.
- Sodium: In the absence of edema, cardiac failure or hypertension, sodium restriction is contraindicated & patient should take no added salt diet.

MANAGEMENT OF COMPLICATIONS IN CRF

ANEMIA

Clinically significant anemia develops when GFR falls below 20-25 ml/min. It is usually normocytic normochromic anemia caused by:

- Reduced erythropoietin production by the kidney
- Reduced red cell survival due to uremia
- Bone marrow depression due to toxic effect of uremia
- Reduced dietary intake of iron due to anorexia.

Clinical features of anemia: dyspnoea on exertion, fatigue

Management:

- Start treatment when hematocrit is <30% with target hematocrit 31-36%.
- Rule out iron and B12 deficiencies.
- Recombinant erythropoietin (Repo) Getz Pharma 2000 units 20-50 units/kg S/C 3-times/week.
- Hypertension is the side effect that develops in about 20% of patients getting erythropoeitin.

HYPERTENSION

Hypertension in CRF results from multiple factors such as:

- Salt and water retention causing volume over load
- Hyper-reninemia
- Sympathetic stimulation causing peripheral and renal vasoconstriction.

Hypertension may develop any time in the course of renal failure even before the serum creatinine is raised.

Glomerular disease is more associated with hypertension than tubulointerstitial disease.

Control of hypertension delays the progression of renal failure.

Treatment

- Salt restrict diet.
- Loop diuretics such as frusemide 40-400 mg/d. Bumetanide (Bumex) has better GI absorption.
- ACE inhibitors are very effective; they control hypertension as well as delay renal failure progression, however they should not be used in patients having creatinine 3 or more until the patient is on dialysis.
- Calcium channel blockers such as verapamil or diltiazem are usually used.
- Beta-blockers may be used.
- Nifedipine and nitroprusside in emergency.
- Dialysis.

HYPERKALEMIA (K > 4.9 mEq)

Due to some adaptive processes potassium level remains normal in CRF until GFR is less than 10 ml/min and the patient becomes oliguric. Once oliguria is present, the adaptive mechanism becomes ineffective.

Predisposing factors for hyperkalemia

- *Exogenous:* K-sparing diuretics, ACE inhibitors, NSAIDs and beta-blockers.
- *Endogenous*: hemolysis, trauma and infection.

Manifestations

Muscle weakness and even paralysis, irritability, and cardiac arrhythmias.

Cardiac manifestations

Bradycardia, AV block, ventricular arrhythmias and cardiac arrest.

- K+ 6 mEq or above: earliest manifestations on ECG.
- K+ 7 cardiac effect usually not significant
- K+ 8 cardiac manifestations always present
  - Tall, peaked P wages and short Q-T interval
  - Prolonged P-R interval
  - Disappearance of P wave
  - Wide QRS complex
  - Ventricular arrhythmias
  - Cardiac arrest

Factors exaggerating ECG changes of hyperlalemia are:

- Low sodium and calcium
- Acidosis and high magnesium

MANAGEMENT

- Dietary restriction of K+
- Avoid drugs that cause hyperkalemia

Prevention of cardiac arrhythmia

- Inj. Calcium gluconate (Calcium Sandoz) 10ml IV slowly within 2-3 minutes.
- Onset within 1-2 min duration of protection 30-60 min.
- Dose can be repeated if no change in ECG after 5-10 min.
- Indication of bradycardia on monitor is an indication to stop the injection.
- It does not change serum potassium level, gives temporary protection and allows time for the measures to shift potassium intracellulary to reduce the risk of arrhythmia.:

Shift the K+ intracellularly

Glucose and insulin

- Insulin facilitates potassium movement into the cell, thus reducing plasma potassium level.
- 10 units of regular insulin plus one ampoule of 50% glucose over a five minute period.
- Another method is to give 500 ml of 10% dextrose water with 15-20 units of regular insulin over one hour.
- Onset is about 30 min and duration of effect 4-6 hours.

Sodium bicarbonate

- Sodium bicarbonate infusion temporarily shifts potassium into the cells, and is especially helpful if the patient has metabolic acidosis.
- Onset within a few minutes and effect lasts upto 2 hours.
- One ampoule of 8.4% NaHCO3 solution (Myelon-84) infused slowly over 5-min. Repeat if necessary within 30 min or add to an IV infusion fluid.
- Loop diuretic is usually combined that increases K loss and prevents sodium retention

Beta 2 – agonists

- Salbutamol parenterally or in nebulized form shifts K intracellularly and lower serum K level.
- Onset is 30 min, duration of effect 2-4 hours and it decreases 0.5-1.5 mEq of K.

Acute reduction of body potassium level

- **Cation exchange resins** such as kayexalate 25-50g mixed with 100ml of 20% sorbitol. It will act within 1-2 hours and effect lasts for 4-6 hours.
- **Dialysis:** life-threatening complications not responding to medical treatment.

RENAL OSTEODYSTROPHY

This is the term used for various forms of bone disease that develop in chronic renal failure i.e. osteomalacia, osteoporosis, secondary hyperparathyroid bone disease (ostetis fibrosa) and osteosclerosis.

- **Osteomalacia:** results from failure of the kidney to convert cholecalciferol (Vit. D) to its active metabolite 1, 25 dihydroxycholecalciferol; deficiency of which leads to diminished intestinal absorption of calcium, hypocalcaemia and reduction in the calcification of osteoid.
- **Hyperparathyroid bone disease**: results from secondary hyperparathyroidism, the parathyroid glands being stimulated by the low plasma calcium.
- **Osteoporosis** results due to malnutrition in chronic renal failure.
- **Osteosclerosis** results from unknown cause & is seen mainly in the sacrum, base of skull and in vertebrae.

CALCIUM, PHOSPHOROUS AND BONE ABNORMALITIES

- As the GFR falls below 25% of normal phosphorous excretion is impaired. Hyperphosphatemia leads to hypocalcemia due to deposition of calcium phosphate in bone, which stimulates secretion of parathyroid hormone (PTH) and increases bone turnover with osteoclastic bone resorption and subperiosteal lesions.
- Most common bone lesion is ostetis fibrosa cystica due to very high PTH. On x-ray lesions are more prominent in distal phalanges and lateral ends of clavicle.
- Osteomalacia develops when PTH level is relatively low but there is decreased mineralization due to decreased absorption of calcium from gut as a result of decreased renal conversion of 25-hydroxycholecalciferol to 1,25-hydroxycholecalciferol.

Clinical features

Bone pain, proximal muscle weakness, fractures, pruritus and extraskeletal calcification.

Treatment

Therapy should be started early in the course of progressive renal failure.

Goal of treatment

1. To maintain serum calcium, phosphorous
2. To prevent hyperparathyroidism
3. To prevent extra-skeletal calcification
4. To maintain normal bone histology.

Strategy

- Treat secondary hyperparathyroidism by correction of hyperphosphatemia.
- Normalization of serum calcium by administration of calcium and activated vitamin D.

Correction of hyperphosphatemia

- Secondary hyperparathyroidismis best treated by reducing the serum phosphate concentration through the phosphate-restricted diet and oral phosphate-binding agents. Calcium carbonate is preferred. Phosphate binder; aluminum hydroxide is used when calcium carbonate can not effectively reduce the phosphorous level.
- Dietary restriction of phosphorous is advised when GFR is less than 50 ml/min. As the GFR falls further, phosphate binder is added that prevents absorption from GI tract.
- Goal is to maintain phosphorous level in between 4-5 mg/dl.
- Calcium carbonate (Tab. Caltrate 500 mg) 500mg-2g orally with meals is effective in most patients as it reduces the bioavailability of dietary phosphorous.
- If phosphate level cannot be maintained between 4-5 mg/dl with $CaCO_3$ or initial phosphorous level is > 7mg/dl, aluminum hydroxide antacide 15-30 ml with meals, chronic use can lead to osteomalacia. Stop $CaCO_3$ if calcium and phosphate calcifications are commonly seen in blood vessels, soft tissues, lungs and myocardium.

Normalization of serum calcium

If hypocalcemia persists after phosphate has been controlled, vitamin D3 may be added. Alfacalcidol (ONE-ALPHA Leo) 0.25μg daily. Vitamin D therapy has disadvantage that it increases gut phosphorous absorption and may therefore exacerbate hyperphosphatemia.

Indications of parathyroidectomy

- Calciphylexis: ischemic necrosis of skin or soft tissue due to vascular calcification
- Severe hypercalcemia
- Severe PTH > 1000

ENDOCRINE ABNORMALITIES

- Amenorrhea in females
- Loss if libido in both sexes due to associated hyperprolactinaemia

CVS DISORDERS

- Hypertension develops in about 80% patients of chronic renal failure.
- Atherosclerosis is common.
- Pericarditis in untreated and stage renal failure.

ACIDOSIS

Decline renal function is associated with metabolic acidosis because kidney is unable to regulate acid-base balance.

INFECTIONS

Both cellular & humoral immunity are impaired and thus increased susceptibility to infection occurs. Urinary tract infections are common.

SKIN ABNORMALITIES:

- Yellow-brown pigmentation of skin occurs due to accumulation of urinary pigments in the skin especially urochrome.
- Pruritus due to accumulation of pigments.

NEUROMUSCULAR DISTURBANCES

Neuropathy: there is demyelination of medullary nerve fibers resulting in:

- Secondary neuropathy – causing paraesthesia
- Motor neuropathy – causing foot drop
- Autonomic neuropathy – causing GIT motility disorders & postural hypotension.

Myopathy results from poor nutrition, hyperparathyroidism, Vit. D deficiency & disorders of electrolyte metabolism.

INDICATIONS FOR DIALYSIS IN CRF

- Uremic symptoms such as pericarditis, encephalopathy, seizures or coagulopathy.
- Fluid overload unresponsive to diuresis.
- Refractory hyperkalemia.
- Severe metabolic acidosis (pH<7.2)
- Serum creatinine about 10 mg/dl and urea 200mg/dl.

Patients typically require hemodialysis 3-times/week.

Complications	Manifestation	Treatment
Pericarditis	• Chest pain and fever • Friction rub • Cardiomegaly on x-ray • Tamponade may develop	Hemodialysis, use minimum heparin as hemorrhagic pericardial effusion may develop.
Metabolic acidosis	• Usually mild until GFR <25/min. • PH is maintained at 7.33-7.37 due to buffering action of calcium carbonate and calcium phosphate stores of bone.	• Protein restriction • Calcium carbonate • Sodium bicarbonate • Bicarbonate should be maintained at 18-20 mEq.
Coagulopathy Platelets normal but prolonged BT	Petechiae, purpura, increased tendency for bleeding during surgery.	• Treatment required in symptomatic patients. • Desmopressin 25µg IV as a single dose before surgery. • Dialysis improves BT but does not normalize.
Infections	Pneumonia and UTI are common infections	Antibiotics
Encephalopathy	Does not occur until GFR is <10-15 ml/min. PTH is believed to one of the uremic toxins. When calcium > 14-15 mg/dl mental status changes start manifesting as lethargy, confusion, coma, asterixis and hyerreflexia. Sensorymotor (gloves and stocking type) and autonomic neuropathy.	Dialysis may improve the symptoms. Early dialysis may prevent neuropathy.
Endocrine	• Impotence • Hypoglycemia or hyperglycemia • Infertility due to anovulation	
CCF	Features of R and L sided heart failure	• Frusemide (Lasix) is the drug of choice, thiazide are not effective below GFR 15 ml/min. • ACE inhibitors are also effective, but should be avoided if the serum creatinine is > 3mg/dl and patient is not on dialysis because of the risk of hyperkalemia and worsening renal function. Once the patient is no dialysis ACE inhibitors can be started. • Digoxin should be used within caution as it is partially excreted through kidney.

TUBULOINTERSTITIAL DISEASE

Tubulointerstitial disease may be acute or chronic.

ACUTE TUBULOINTERSTITIAL NEPHRITIS

Acute disease is most commonly associated with hypersensitivity reaction to drugs. Patient presents with fever, arthalgia, skin rashes and acute oliguric or non- oliguric renal failure with eosionophilia and eosinophiluria.

Common causes

Penicillins, cephalosporins, NSAIDs, allopurinol, sulphonamides, rifampicin, diuretics, cimitidine and phenytoin.

Management is withdrawal of offending drug, steroids and dialysis. Prognosis is good and few patients may develop significant interstitial fibrosis.

CHRONIC TUBULOINTERSTITIAL DISEASE

Chronic tubulointerstitial disease may progress from acute disease or progressive without obvious acute insult resulting in interstitial fibrosis and tubular atrophy leading to chronic renal failure.

Main causes

Obstructive uropathy

Obstructive uropathy such as prostate hypertrophy, bilateral ureter stone, carcinoma of cervix, colon, bladder and retroperitoneal fibrosis.

Vesicoureteral reflux

Urine passes passes retrograde from the bladder to the kidneys during voiding as a result of incompetent vesicoureteral sphincter. Patients are adolescents or young adults with hypertension, renal insufficiency and history of urinary tract ifections as a child.

Analgesics

Chronic ingestion of 1g/day for 3 years is the typical amount needed for renal dysfunction.

Heavy metals

Chronic lead and cadmium exposure usually in occupational workers.

Diabetes and sickle cell disease

Clinical features

Polyuria due to inability to concentrate urine by the damaged tubules.

Treatment

Treatment or avoidance of the cause.
Supportive measures if end stage renal disease.

HYPERURECEMIC (GOUTY) NEPHROPATHY

Hyperurecemia and hyperuricosuria may cause two patterns of disease:

- Acute hyperurecemic nephropathy
- Uric acid stone formation (discussed in renal stones)

ACUTE HYPERURECEMIC NEPHROPATHY

This is well- recognized cause of acute renal failure mainly in patients of myeloproliferative or lymphoproliferative disease when there is rapid cell lysis after starting chemotherapy and radiotherapy releasing large amounts of nucleoproteins and increased uric acid production.

Renal failure develops due to intrarenal and extrarenal obstruction caused by deposition of uric acid crystals in the collecting ducts, pelvis and ureters. Patient presents with oliguria, uremia, and colicky flank pain.

Prevention

- Proper hydration state.
- Allopurinol 100-200mg three times daily for 5 days is given prior and continuing throughout treatment with radiotherapy and chemotherapy.
- Keep urine alkaline with sodium bicarbonate because uric acid is more soluble in alkaline medium.

Treatment

- Forced alkaline diuresis with IV sodium bicarbonate plus acetazolamide.
- Continue allopurinol.
- Dialysis may be required in severe oliguric or anuric patients to lower plasma uric acid level.
- Percutaneous nephrostomy to relieve obstruction by stone may be required.

RENAL REPLACEMENT THERAPY

The aim of renal replacement techniques is to mimic excretory functions of normal kidney, including excretion of nitrogenous waste products, maintenance of normal electrolytes concentrations, and maintenance of a normal extracellular volume.

HEMODIALYSIS

In hemodialysis blood from the patient is pumped through an array of semipermeable membranes (dialyser) which bring the blood into close contact of dialysate. The plasma biochemistry changes towards that of the diasylate due to diffusion of molecules down their concentration gradient.

Access for hemodialysis

Adequate dialysis requires a blood flow of at least 200ml/min. The most reliable long- term way of achieving this is surgical construction of an arterio-venous fistula (AV fistula) using the radial or brachial artery and the cephalic vein. This results in distension of the vein and thickening (called arterialization) of its walls, so that after 6-8 weeks large – bore needles may be inserted to take blood to and from the dialysis machine.

Frequency and duration

Frequency and duration of dialysis are adjusted to achieve adequate removal of uremic metabolites and to avoid excessive fluid overload between dialysis sessions. An adult patient of average size usually receives 4-5 hours treatment 3 times a week.

Complications of hemodialysis

- Hypotension during dialysis.
- Anaphylactic reaction to the drug used to sterilize dialyzers (rare).
- Hard water syndrome
- Hemolytic reaction
- Air embolism
- *Dis- equilibrium syndrome:* rapid change in plasma osmolality in hemodialysis (i.e. rapid correction of uremia) causes nausea, vomiting, restlessness, headache, hypertension, myoclonic jerking, seizure and coma in severe cases(due to cerebral edema).
- Dialysis dementia
- Osteomalacia and microcytic anemia due to aluminium contamination of dialysate solution.
- Hepatitis B and C
- Anorexia
- Complications of heparinization

PERITONEAL DIALYSIS

Peritoneal dialysis utilizes the peritoneal membrane as a semipermeable membrane, avoiding the need for dialysis machine.

A tube is inserted into the peritoneal cavity through the anterior abdominal wall. Diasylate solution is run into the peritoneal cavity usually under gravity. Urea, creatinine, phosphate and other uremic toxins pass into the diasylate down their concentration gradients. Excess water comes into the peritoneal cavity by the osmotic process. The fluid is changed regularly to repeat the process.

Advantages

- Greater patient autonomy.
- Can be performed in hemodynamically unstable patients because these patients are not suitable for hemodialysis that itself causes hypotension.
- Decreased symptomatic swings observed in hemodialysis
- Poorly dialyzable compounds such as phosphates are better cleard which permits less dietary restriction.

Disadvantage

Peritonitis

Less efficient than hemodialysis, not achieving good biochemical control.

RENAL TRANSPLANTATION

Successful renaltransplantation offers the potential for almost complete rehabilitation in end – stage renal failure. Donor may be living close relative or cadaveric (patients with brain death).

Immunosuppression therapy is given for a long period to prevent graft rejection with corticosteroids and cyclosporin, azathioprin and tacrolimus.

Complications

1. Stenosis of arterial anastomosis
2. Increased risk of infections due to immuosuppression therapy.
3. Increased risk of lymphoma and skin cancer.
4. Recurrence of disease that caused renal failure such as Good pasture's syndrome and focal segmental glomeruloscelosis.
5. Complications of immunosuppresant drugs as following:

- *Corticosteroids:* weight gain, skin striae, diabetes, osteoporosis and hypertension.
- *Cyclosporin:* nephrotoxicity, rash, tremor, increased hairiness (hirsutism), gingival hyperplasia, hypertension and diabetes.
- *Azathioprine:* bone marrow suppression and hepatotoxicity.
- *Tacrolimus:* neurotoxicity and hepatotoxicity.

Prognosis

About 80% grafts survive for 5-10 years and 60% for 10-30 years.

POLYCYSTIC KIDNEY DISEASE

Infantile polycystic disease

It is a rare disease, inherited as an autosomal recessive trait. It is associated with hepatic fissures and is often fatal in the first year of life due to renal failure or hepatic failure.

Adult polycystic disease

It is a common hereditary disease, inherited as an autosomal dominant trait, males and females are equally effected. Age of onset is 20-40 years. Family history is positive in 75% of cases.It is characterized by development of multiple renal cysts that may be associated with hepatic cysts (in 40-60%), intracranial berry aneurysm formation(in 10-15%) and mitral valve prolapse. Pancreatic and splenic cysts may also occur.

> It is a common short case. If you are asked to examine the patient of hypertension; always palpate kidneys for polycystic kidney disease and compare pulses of upper and lower limbs for coarctation of aorta.

ADULT POLYCYSTIC KIDNEY DISEASE

Clinical features

- Patient of polycystic kidney disease may present in a variety of ways as following.
- Often asymptomatic until late in the life.
- After the age of 20 years there is an insidious onset of hypertension (in > 50%) which may or may not be associated with impairment of renal function.
- Acute loin pain and /hematuria (microscopic or gross) due to hemorrhage into cyst, cyst infection or urinary stone formation.
- Loin or abdominal discomfort due to increasing size of the kidneys.
- Complications of hypertension such as IHD, stroke.
- Complications of hepatic cysts.
- Subarachnoid hemorrhage due to rupture of berry aneurysm.
- Symptoms of uremia.

On examination

Palpable kidneys on examination.

> **ADULT POLYCYSTIC KIDNEY DISEASE**
>
> ***Clinical features***
>
> - Vague discomfort in loin or abdomen due to increasing mass of renal tissue.
> - Acute loin pain or renal colic due to hemorrhage into a cyst
> - Hypertension
> - Hematuria
> - Urinary tract infection
> - Renal failure
>
> ***Other features and associations***
>
> - Often one or both kidneys may be palpable.
> - About 40-60% of patients with polycystic kidney disease have hepatic cysts, but disturbance of liver function is rare.
> - Berry aneurysms of cerebral vessels are an associated feature and about 10% of patients have subarachnoid hemorrhage.
> - Mitral and aortic regurgitations are frequent but rarely severe.
> - Colonic diverticular and abdominal wall hernias are recognized associations.
> - There is gradual reduction in renal function.

Investigations

- *Hemoglobin:* it is maintained due to production of erythropoietin in cysts.
- *Urine analysis*: hematuria, mild proteinuria.
- *Ultrasound kidneys*: diagnostic criteria for autosomal dominant polycystic kidney disease on ultrasound is following:
  - Two or more cysts in patients under age 30.
  - Two or more cysts in each kidney in patients age 30-59.
  - Four or more cysts in each kidney in patients age 60 or over.

Management of complications

Abdominal pain or flank pain: bed rest, analgesics in acute and cyst decompression in chronic pain.

Hematuria: gross hematuria results from rupture of cyst into renal pelvis or renal stone or UTI. It resolves usually within 7 days with bed rest and hydration.

Renal infection: patient presents with fever, flank pain and leukocytosis. Blood culture may be positive but urinanalysis may be normal because the cyst does not communicate directly with the urinary tract. CT scan may be helpful. Cyst penetrating antibiotics such as quinolones, Septran or chloramphenicol are given parenterally for 2 weeks then orally for long –term.

Kidney stones: about 20% of patients have kidney stones of calcium oxalate. Hydration is advised to prevent stone formation.

Hypertension: cyst induced ischemia activates rennin- angiotensin system and cyst decompression can lower blood pressure temporarily. Antihypertensives are used to strict blood pressure control to prevent its complications.

Cerebral aneurysm: screening angiography for aneurysm in circle of Willis is not advised unless the patient has family history of aneurysm or he is going for elective surgery in which there is high risk of developing hypertension.

Other complications: mitral valve prolapse, aortic aneurysm, aortic valve abnormalities and colonic diverticula.

Prognosis

Renal failure can not be prevented with medical treatment. Treatment of hypertension and low protein diet may slow the progression of disease. Screening of the family members with ultrasound kidney is recommended.

MEDULLARY SPONGE KIDNEY

This benign disorder is present at birth and not diagnosed until fourth or fifth decade. Kidneys have a marked irregular enlargement of the medullary and interpapillary collecting ducts. This is associated with medullary cysts that are diffuse giving a "Swiss cheese" appearance in these regions.

Clinical features

- Hematuria: gross or microscopic.
- Recurrent UTI.
- Renal stone formation.and nephrocalcinosis.
- Distal renal tubular acidosis
- Decreased urinary concentrating ability.

Investigations

Intravenous pyelography (IVP): it shows striations in the papillary portions of the kidney produced by accumulation of contrast in dilated collecting ducts.

Treatment

- No medical curative treatment.
- Adequate fluid intake to prevent stone formation.
- If hypercalciuria present then give thiazide diuretics that decrease calcium excretion.
- Alkali therapy is advised if there is renal tubular acidosis.

URINARY TRACT INFECTIONS (UTI)

Urinary tract infection is associated with multiplication of organisms in the urinary tract and is defined by the presence of more than a hundred thousand organisms per ml in midstream sample of urine. UTI is common in women and uncommon in men.

ORGANISMS CAUSING URINARY TRACT INFECTION

Organism	*Approximate frequency*
E.Coli	68%+
Proteus	12%
Klebsiella	4%
Enterococcus fecalis	6%
Staphylococcus saprophyticus or epidermidis	10%

PATHOGENEIS

Routes of spread

1. Ascending transurethral route
2. Bloodstream
3. Lymphatics
4. Direct extension (from vesicocolic fistula)

Ascending transurethral route

- Periurethral area is heavily colonized with bacteria derived from fecal flora. Colonization may be facilitated by lack of personal hygiene, wearing of sanitary towels & local infections (e.g. vaginitis)
- Bacteria are transferred along the urethra to the bladder, which is facilitated by cathetrization or sexual intercourse. Transfer along the short urethra of female is easy, while the longer male urethra protects against transfer of bacteria to the bladder.
- Multiplication of bacteria occurs in the bladder, from where they can reach the ureters and kidneys easily, facilitated by vasicoureteric reflux and dilatation of hypotonic ureters.

TYPES

Uncomplicated UTI: when infection occurs in a patient with functionally normal urinary tracts is called uncomplicated UTI.

Complicated UTI: when infection occurs in a patient with abnormal urinary tracts e.g. with stones or associated disease e.g. diabetes mellitus, which themselves cause kidney damage may be made worse with infection, it is called complicated UTI.

URINARY TRACT INFECTION UNCOMPLICATED AND COMPLICATED

Uncomplicated

- Anatomically and physiologically normal urinary tract, normal renal function
- No associated disorder which impairs defense mechanism.

Complicated

- Abnormal urinary tract e.g. obstruction, calculi, vesico-ureteric reflux, neurological abnormality, indwelling catheter, chronic prostatitis, cystic kidney, analgesic nephropathy, renal scarring
- Impaired renal function
- Associated disorder which impairs defense mechanisms (e.g. diabetes mellitus)

CLINICAL PRESENTATIONS OF URINARY TRACT INFECTION

- Asymptomatic bacteriurea
- Symptomatic acute urethritis and cystitis
- Acute prostates
- Acute pyelonephritis
- Septicaemia (usually Gram-negative bacteria)

LOWER URINARY TRACT INFECTION

This includes urethritis, cystitis and prostatitis

Clinical features

- Increased frequency of micturition
- Dysuria: Scalding pain is felt in the urethra during micturiton
- Suprapubic pain during and after micturition in case of cystitis.
- Intense desire to pass more urine after bladder has been emptied, due to spasm of the inflamed walls.
- Urine may have unpleasant odor and appear cloudy.

Investigations

- Urine culture & sensitivity
- Urine D/R: more than 100,000 of the same organism/ml indicate UTI.

Management

- High fluid intake (2 liters daily)
- Potassium citrate mixture (Citralka) 10 ml three times daily in half glass of water. It alkalinizes the urine and relieves dysuria.
- Antibiotics:
  - Ciprofloxacin (T. Ciproxin 250-500mg) 12 hourly for 1-3 days OR
  - Norfloxacin (T. Noroxin 400mg) 12 hourly for 1-3 days.

> **PROPHYLACTIC MEASURES TO BE ADOPTED BY WOMEN WITH RECURRENT URINARY INFECTIONS**
> - Fluid intake of at least 2l/day
> - Regular emptying of bladder 3h intervals by day and before retiring)
> - Ensure complete emptying of bladder Double micturition if reflux present (The patient should be advised, particularly before retiring for the night, to empty the bladder and then attempt to empty the bladder and then attempt to empty the bladder a second time approximately 10-15 minutes later)
> - Emptying bladder before and after intercourse.
> - Application of 10% cetrimide cream to periurethral area before intercourse.

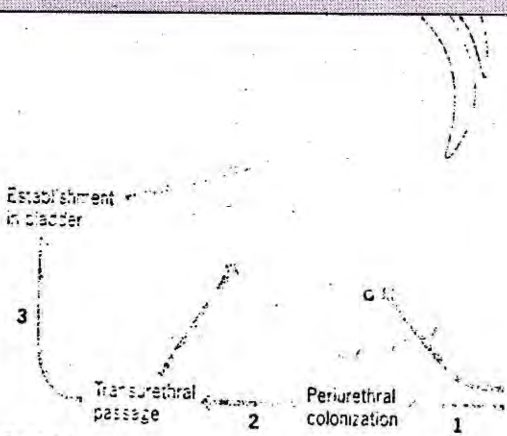


Fig 9.19
Ascending infection of the urinary tract

UPPER URINARY TRACT INFECTION

Acute Pyelonephritis

Mostly it results from ascending infection from bladder.

Clinical Features

- *Loin pain:* Sudden onset of pain in one or both loins, radiating to the iliac fossae and suprapubic area.
- *Urinary symptoms:* dysuria and frequent passage of small amounts of scalding cloudy urine due to associated cystitis.
- *Fever:* 38-40oC, may be with rigors and vomiting.
- *Tenderness* presenting the renal angle and lumbar region.

Investigations

- Blood CP – leucocystosis
- Urine D/R – numerous plus cells and organisms.
- Urine – C/S

Differential diagnosis

Acute appendicitis, salpingitis, cholecystitis, diverticulitis, perinephric abscess

Complications

- Sepsis and shock
- Emphysematous pyelonephritis by gas producing organisms.
- Pyonephrosis (abscess formation).
- Chronic pyelonephritis.

Management

- *Antibiotics:* Ciprofloxacin (T. Ciproxin 250, 500mg) 750mg 12- hourly for 21 days. Ofloxacin or Septran may be used.
- *Symptomatic*: paracetamol for fever, potassium citrate (Citralka) for dysuria.

Chronic pyelonephritis

This results from recurrent urinary tract infection due to vesicouretric reflux and due to infection acquired in infancy or childhood.

Vesicoureteric reflux

Normally the vesicouretric junction acts as a one way valve i.e. no reflux of urine into ureters during bladder contraction. If this valve is incompetent, bladder voiding being associated with variable reflux of a jet of urine up the ureters.

A secondary consequence is incomplete bladder emptying as refluxed urine returns to the bladder after voiding. This incomplete bladder emptying predisposes to infection and the reflux of infected urine leads to kidney infection & damage.

Pathology

Gross scarring of the kidneys, which may be reduced in size with narrowing of the cortex and medulla may be seen. This atrophy of the kidney reduces the renal functions.

Clinical features

- Mostly there are no direct symptoms.
- Patient may consult the doctor for hypertension or symptoms of uremia.

Investigations

1. IVP: shows
   - Kidneys are reduced in size
   - There are localized contractions of renal substances associated with clubbing of the adjacent calyces.
2. *Renal ultrasound:* as an alternative to IVP to identify obstruction, cysts or calculi.
3. *Urine culture:* mostly E.coli
4. *Cystoscopy* to identify any obstruction to the urinary outflow.
5. *Micturiting cystourethrogram:* demonstrates vesicoureteric reflux.
6. *Renal function tests*: e.g. blood urea, creatiine, serum electrolytes and creatinine clearance.

Management:

- Chronic infection is difficult to eradicate
- An antibiotic to which organism is sensitive should be given for 3-6 months. Usually ciprofloxacin (T. Ciproxin 250, 500mg) 750 mg 1- hourly is advised.
- Control hypertension.
- Remove if there is some obstruction.
- Unilateral nephrectomy when pyonephrosis develops.
- Vesicoureteric reflux disappears spontaneously in adult age.

PROSTATITIS

ACUTE PROSTATITS

Acute bacterial prostatitis is usually caused by E. coli, pseudomonas or enterococcus.

Clinical features

- Perineal pain, dysuria.
- Varying degree of urinary obstruction or retention due to swelling of prostate.
- Fever and tender prostate on examination by per rectal examination. Prostatic massage is contraindicated in acute prostatitis.

Investigations

- Blood CP: leukocytosis with predominant neutrophils.
- Urinalysis: pyuria, bacturia and hemtaturia.
- Urine culture and sensitivity may demonstrate organism.

Treatment

- Intravenous ampicillin and aminoglycosides until report of culture is available, then continue oral antibiotics (usually ciprofloxacin) for 4-6 weeks.
- In case of urinary retention urinary catheterization is contraindicated; and percutaneous suprapubic puncture is required.

CHRONIC BACTERIAL PROSTATITIS

Organisms are same as that of acute prostatitis. Patient may be asymptomatic or presents with low back pain, dysuria, perianal pain.

Urinalysis is normal. Culture of the secretion obtained from prostatic massage is necessary for diagnosis.

Septran is associated with best cure rate. Other effective drugs are erythromycin, cephalexin and quinolones such as ciprofloxacin for 6-12 weeks.

ACUTE EPIDIDYMITIS

Acute epididymitis may be sexually transmitted due to N. gonorrhea or chlamydia trachomatis or non-sexually transmitted associated with UTI and prostatitis.

Clinical features

- Pain in scrotum and may radiate along the spermatic cord or to the flank.
- Symptoms of UTI may be present.
- Fever and scrotal swelling are present on examination.

Differential diagnosis

- Acute epididymitis should be differentiated from testicular torsion that occurs in peripubertal males or young adults with acute onset of symptoms and negative urinalysis.
- Testicular tumors are painless.

Investigations

- *Blood CP*: leukocytosis with neutrophil predominant.
- *Gram staining* of smear of urethral discharge in sexually active patient may show gonococci, or WBC without organism representing nongonococcal infection such as C. trachmatis.
- In non- sexually transmitted variety urinalysis shows pyuria, bacteriuria and hematuria. Urine culture demonstrates offending organism.

Treatment

- Bed rest.
- Scrotal elevation.
- Sexually transmitted: antibiotics for 10-21 days.
- Non- sexually transmitted: antibiotics for 21-28 days

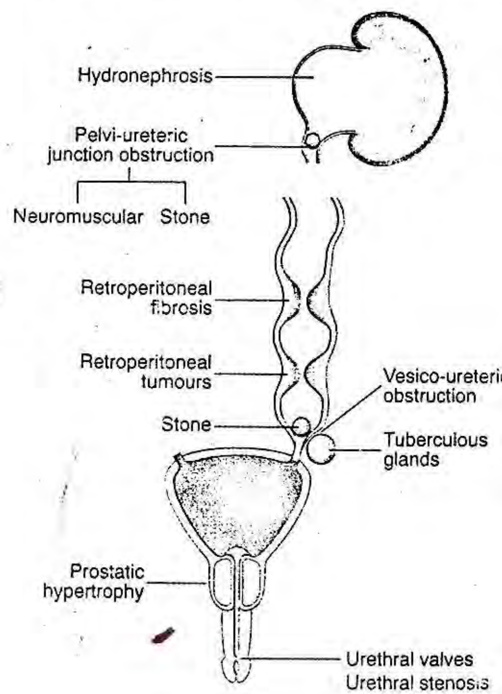
URINARY TRACT OBSTRUCTION

Obstruction to the flow of urine from kidney causes urinary stasis and an increase in pressure above the obstruction, which in turn predisposes to infection, stone formation, hydronephrosis and renal failure. Obstruction is more common on the following sites:

- Pelviureteric junction
- Bladder neck
- Urethra

Treatment is relieving the obstruction.

Prognosis depends on whether the obstruction is partial or complete and duration of obstruction. Infection leads to more rapid renal loss. Complete obstruction of several weeks lead to irreversible or partially reversible renal damage.



RENAL AND VESICAL CALCULI

Renal and bladder stones are very common in Pakistan due to hot environment; therefore it is a common topic for MCQs and viva.

Types and frequency of renal stones

Type of renal stone	*Approximate frequency (%)*
Calcium oxalate	65
Calcium phosphate	15
Magnesium ammonium phosphate	10-15
Uric acid	3-5
Cystine	1-2

Risk Factors for Renal stone formation

Risk factor	*Type of stone*
Obstruction of urinary tract	Phosphate
Infection of urinary tract	Phosphate
Repeated dehydration (occupation, climate)	All types
Hypercalciuria	Calcium oxalate
Hypercitraturia	Calcium
Inherited disorders	
Cystinuria	Cystine
Xanthinuria	Xanthine
Gout, myeloproliferative disorders	Uric acid
Medullary sponge kidney	Calcium

PREDISPOSING FACTORS

- A chemical composition of urine that favours stone cystallization.
- The production of concentrated urine as a consequence of dehydration.
- Impairment of inhibitors that prevent crystallization in normal urine.

Hypercalcemia

The common causes of hypercalcemia leading to some formation are:

- Primary hyperparathyroidism
- Excessive vitamin D ingestion
- Sarcoidosis
- Multilpe myeloma

Hypercalciuria

- Hypercalcemia
- An excessive dietary intake of calcium
- Excessive resorption of calcium from the skeleton, such as occurs with prolonged immobilization.
- Idiopathic hypercalciuria: it may be because of increased absorption of calcium from the gut or leakage of calcium from renal tubules.

Hyperoxaluria

- It results from inborn errors of oxalate metabolism that causes increased endogenous oxalate biosynthesis.
- Other causes of hyperoxaluria are:
  - Excess ingestion of foodstuffs high in oxalate such as spinach, rhubarb and tea.
  - Dietary calcium restriction with compensatory increased absorption of oxalate.
  - Gastrointestinal disease e.g. Crohn's disease, usually with intestinal resection, associated with increased absorption of oxalate from the colon.

Hyperuricemia and hyperuricosuria

Uric acid is the end product of purine metabolism. Hyperuricemia can occur as a primary defect in idiopathic gout or secondary consequence of increased cell turnover such as in myeloproliferative disorders. Increased uric acid excretion leads to stone formation. Hyperuricosuria may be without hyperuricemia. Dehydration alone may cause uric acid stone formation.

Urinary tract infection

Infection with proteus mirabilis may lead to magnesium ammonium phosphate stone formation.

Primary renal diseases

- Medullary sponge kidney leads to hypercalciuria and stone formation.
- Renal tubular acidosis leads to persistently alkaline urine formation that causes stone formation.

CONDITIONS ASSOCIATED WITH HYPERCALCIURIA AND HYPEROXALURIA

Hypercalciuria

Causes of hypercalcaemia
- Hyperparathyroidism, vitamin D excess, myeloma, sarcoidosis etc.

Hypercalciuria without hypercalcemia
- High intake (daily produce)
- Renal tubular acidosis
- Cushing's syndrome
- Prolonged immobilization
- Idiopathic
  Increased absorption from gut
  Reduced renal tubular reabsorption

Hyperoxaluria
- High intake (fruit and vegetables)
- Increased absorption
  Ileal diseas
  Low calcium diet

Causes of bladder stone formation
- Bladder outflow obstruction e.g. urethral stricture, neuropathic bladder, prostatic obstruction.
- The presence of foreign body e.g. catheters, non-absorbable sutures.

CLINICAL FEATURES
Clinical features of urinary tract stones may be:
- Asymptomatic
- Pain-renal colic
- Hematuria
- Urinary tract infection
- Urinary tract obstruction

Pain
Patients with renal stones commonly present with pain having following features
- Site: loin or back
- Nature: dull
- Character: intermittent
- Aggravated by: movement

Ureteric colic
Ureteric colic occurs when a stone enters the ureter and either obstructs it or causes spasm during its passage down the ureter. It has the following features:
- Site: loin
- Radiation: radiates round the flank to the groin and often into the tests or labium in the sensory distribution of first lumbar nerve.
- Intensity: severe
- Character: colicky
- Associated with: pallor, severe restlessness, sweating and often vomiting. Frequency, dysuria an dhematuria may also occur.

INVESTIGATIONS
- Urinalysis: determines pH, hematuria, infection, and types of crystals. Normal urine pH is 5.85; persistent urinary pH below 5.0 is suggestive of uric acid or cystine stone. In contrast a persistent pH above 7.5 is suggestive of struvite infection stone.
- Blood urea, electrolytes, serum creatinine, serum calcium, phosphate and uric acid.
- Plain x-ray abdomen
- Ultrasound kidneys.
- IVP (now called intravenous urography IVU)

Evaluation of patient with recurrent stone formation
- A 24- hour urinary collection for volume, urinary pH, calcium, uric acid, oxalate, phosphate and citrate excretion.
- Serum parathyroid hormone.

MANAGEMENT
Medical treatment for loin pain or renal colic:
- High fluid intake
- Bed rest
- Application of warmth to the site of pain
- Analgesics e.g. pethidine 100 mg I/M or diclofenac sodium (Voren) I/M.
- Antispasmodic: e.g. atropine sulphate (Buscopan, spasler etc) I/V.
- Excessive fluid intake.
- Restriction of salt and protein (avoid animal protein).

TREATMENT OF CONDITIONS CAUSING RENAL STONES

Hypercalcemia and hypercalciuria

- Cellulose phosphate reduces intestinal absorption of calcium.
- Avoid vit. D preparations
- Avoid high calcium foods e.g. milk
- Thiazide diuretics decrease renal excretion of calcium (for hypercalciuria). Salt restriction is also advised.
- Surgery of parathyroids if hyperparathyroidism.

Hyperuricosemia and uricosuria

- Purine dietary restriction
- Allopurinol.

Hyperoxaluria

- Increased fluid intake
- Restrict dietary oxalate.
- Add calcium carbonate

Other stones

- For phosphate stones, acidify the urine by giving ammonium chloride (because they are formed only in alkaline urine).
- For cystine & urate stone: alkaline the urine by sodium bicarbonate

Struvite stones

These are magnesium- ammonium- phosphate stones, common in women with recurrent urinary tract infection. Frequently they are large staghorn calculi. Urinary pH is high. These stones are formed due to infection with urease producing organisms such as proteus, pseudomonas, klebsiella, staphylococcus and mycoplasma but not E.coli.

SURGICAL TREATMENT

Indications

- Persistent pain
- Frequent bouts of severe pain
- Anuria
- Hydronephrosis

Type of operation

Lithotripsy:

Lithotriptor is an equipment applied to the body surface by which shock waves are generated under and focused. Most of the fragments then pass spontaneously via the urethra.

Open operation:

- Nephrolithotomy for renal calculi
- Pyelolithotomy for stones in renal pelvis
- Ureterolithotomy for ureteric stones

Choice of intervention

Ureterral stones

1. Stones less than 6 mm usually pass spontaneously. Observe for 6 weeks with treatment of pain.
2. If there is no spontaneous passage of stone then we have two choices:
   - Uretroscopic stone extraction
   - Extracorporal shock wave lithotripsy (ESWL)

Renal stones

1. Growing or symptomatic renal stones require intervention. Renal stones < 3cm are best treated with lithotripsy.
2. Stones located in the inferior calyx or larger stones are treated with percutaneous nephrolithotomy.

RENAL TUBULAR ACIDOSIS (RTA)

This term is referred to systemic acidosis caused by impairment of the ability of the renal tubules to maintain acid base balance. There is either failure of reabsorption of bicarbonate in the proximal tubule or acidification of the urine in the distal tubule. There may be little or no overall reduction in renal function. Renal tubular acidosis may be due to gene defect or due to diseases causing chronic interstitial nephritis. Some drugs and toxins may be responsible.

TYPES

There are four types of RTA as following:

Type 1 (Distal) Renal tubular acidosis

In this condition the ability to form a very acid urine is lost, and the urine pH cannot be reduced to less than 5.5 even in the presence of severe systemic acidosis. The defect is due to failure of collecting dusts to secrete hydrogen ions. There are two types of distal acidosis:

- In complete distal RTA there is persistent hyperchloremic acidosis.
- In incomplete distal RTA the plasma bicarbonate is normal, but the urine pH does not fall to less than 5.5 after ammonium chloride administration.

Characteristic features

- Acidosis
- Hypokalemia
- Inability to lower the urinary pH below 5.5 despite systemic acidosis.
- Low urinary ammonium production.
- Low urinary citrate
- Hypercalciuria

The abnormalities result in osteomalacia, renal stone formation and recurrent UTI (due to hypercalciuria).

Treatment

Sodium bicarbonate, potassium supplements and citrate. Thiazide diuretic are also effective.

Causes of distal renal tubular acidosis	
Primary Idiopathic **Genetic** Familial Marfan's syndrome Ehler- Danlos syndrome **Nephrocalcinosis** Chronic hypercalcemia Medullary sponge kidney **Hypergammaglobulinaemic states** Amyloidosis* Cryoglobulinaemia Cirrhosis **Drugs and toxins** Amphotericin B Lithium carbonate	**Autoimmune** Sjogren's syndrome Thyroiditis Autoimmune hepatitis Primary biliary cirrhosis **Urinary tract obstruction** **Sickle cell anemia** **SLE** **Renal transplant rejection**

Type 2 (proximal) renal tubular acidosis

This very rare condition in adults is caused by failure of sodium bicarbonate reabsorption in the proximal tubules.

Characteristic features

- Acidosis
- Hypokalemia
- Inability to lower the urinary pH below 5.5 despite systemic acidosis.
- Appearance of bicarbonate in the urine despite as subnormal plasma bicarbonate.

Treatment

Sodium bicarbonate

Causes of proximal renal tubular acidosis	
• Cystinosis • Tyrosinemia • Wilson's disease • Glycogen storage disease • Pyruvate carboxylate deficiency • Multiple myeloma	**Vitamin D deficiency** Hyperparathyroidism **Toxins and drugs** Carbonic anhydrase inhibitors Lead Cadmium Mercury Uranium Copper Outdated tetracycline

Type 3 renal tubular acidosis

It is a combination of type 1 and type 2

Type 4 renal tubular acidosis

It is the most common type of RTA and is also called hyporeninamic hypoaldosteronism.

Characteristic features

- Acidosis
- Hyperkalemia
- Mild chronic renal insufficiency caused by tubulo-intestitial disease.
- Plasma rennin and aldosterone are low

Management

Fludrocortisone, sodium bicarbonate and diuretics.

RTA	Urine pH	Serum potassium
Type I	> 5.5	Low
Type II	< 5.5	Low
Type III	< 5.5.	Normal
Type IV	< 5.5	High

RENAL CELL CARCINOMA

Renal cell carcinoma or hypernephroma arises from proximal tubular epithelium, the average of presentation is 55 years. Cause is unknown; cigarette smoking is the significant risk factor. Von Hippel- Lindau disease (an autosomal dominant disorder) bilateral renal cell carcinoma are common. Renal cell carcinoma may be single, multiple or occasionally bilateral.

Clinical features

- Hematuria (in 60%) is the most common presentation. It may be gross or microscopic.
- Flank pain and abdominal mass in 30%.
- Triad of flank pain, hematuria and mass is present in 10-15% cases.
- Symptoms of metastatic disease such as cough, bone pain occur in 20-30% of cases.

Metastasis

Regional lymph node, bone, lung and liver.

Investigations

- Ultrasound kidneys: show mass
- CT scan: required to assess spread of tumor
- Chest x-ray: to assess the metastasis
- CT scan and bone scan: to assess involvement of bone.

Management

- Removal of the affected kidney, along with adrenal gland and regional lymph nodes for localized non-metastatic tumor.
- Radiotherapy relieves pain due to metastasis.
- Medroxyprogresterone may slow the metastasis.
- Five year survival for tumors confined to the renal capsule 90-100% while 0-15% when lymph nodes are involved.

Syndromes associated with renal carcinoma

Findings	%	Comments
Raised ESR	55	Changes in serum proteins associated with many tumours
Hypertension	37	Secretion or rennin by tumour
Anaemia	36	Depression of erythropoiesis +/- haematuria
Weight loss	34	Tumour products depress appetite
Pyrexia	17	Circulating pyrogens
Abnormal liver function	14	This may disappear after nephrectomy
Raised alkaline phosphatase	9	Secreted by tumour?
Hypercalcaemia	5	Parathyroid hormone like peptide secretion by tumour
Polycythaemia	4	Erythropoietin secretion
Neuromyopathy	3	Tumour-associated antibodies to nerve tissue
Amyloidisis	2	Possibly associated with immunological reactions to the tumour

BENIGN PROSTATIC HYPERTROPHY (BPH)

- This is mot commonly found in men over 60 years.
- Clinically present with urinary flow obstruction. Acute urinary retention may occur if gland suddenly enlarge in size due to infection or congestion. Hematuria due to urethral bleeding may be the presenting symptom.
- On per rectal examination prostate may feel large, elastic and uniform in consistency.
- Ultrasound prostate shows large prostate.
- Alpha-blockers such as doxazocin (Cardura 2mg) initially 1mg once daily then increasing to 2mg once daily may improve the symptoms of urinary outflow obstruction.
- Transurethral resection of prostatic tissue is the treatment of choice.

PROSTATIC CARCINOMA

- Symptoms are similar to BPH.
- On per rectal examination prostate is hard and medium sulcus is obliterated.
- Spread of tumor is often associated with increased serum prostate specific antigen (PSA) which acts as tumor marker.
- Local invasion is checked by ultrasound.
- Screening for metastasis includes measurement of serum PSA, bone scan, x-rays of bone and chest and liver function tests.
- Management is radical prostectomy, radiotherapy and androgen deprivation by estrogen (stillboestrol) or orchidectomy.

TESTICULAR CARCINOMA

- Peak age is 25-35 years. The lesion may be seminoma or teratoma.
- Seminomas present as painless, often uniform, rapid enlargement of testes. Teratoma causes more nodular changes and secrete chorionic gonadotrophin that causes gynaecomastia. Some caes may present with metastasis.
- CT scan of abdomen: to look for involvement of regional lymph node.
- Chest x-ray and LFTs are performed as screening of metastasis.
- Treatment: tumor removal, radiotherapy, chemotherapy (cisplatin and bleomycin).
- Tumor markers such as alfa-fetoprotein, human chorionic gonadotrophin and LDH are of help in assessing response to treatment and for monitoring patients in remission.

BLADDER CANCER

Urinary bladder cancer is the second most common urologic cancer, more common in men and mean age at diagnosis is 65 years. Cigarette smoking and exposure to industrial dyes or solvents are risk factors. Majority are transitional cell carcinomas.

Clinical features

- Hematuria: gross or microscopic, chronic or intermittent (85-90%).
- Urinary frequency, urgency.
- Hepatomegaly and supraclavicular lymphadenopathy may be present with metastatic disease. Lymphedema of lower limb may be present if metastasis involves pelvic lymph nodes.

Investigations

- Urinalasysis: hematuria.
- Blood CP: anemia
- Urine cytology (80-90%) sensitivity.
- IVP, ultrasound CT or MRI.
- Cystourethroscopy and biopsy.

Treatment

- Surgical removal of bladder
- Intravesical chemotherapy
- Radiotherapy
- Chemotherapy.

RHEUMATOLOGY AND BONE DISEASES 7

EXAMINATION OF JOINTS

General principles

Certain general rules apply to the examination of all joints and they can be summarized as following:

1. Look (inspection)
2. Feel (palpation)
3. Move (passive movement)

LOOK (INSPECTION)

Always compare with the joint of opposite side.

Skin

- *Erythema:* it indicates underlying inflammation and suggests active arthritis or infection.
- *Scar:* look scar of previous surgery or trauma.
- *Rash:* such as vasculitic or psoriatic rash.

Swelling

Swelling of the joint may be due to:

- Effusion, synovial inflammation or synovial hypertrophy.
- Bony overgrowth at the joint margin.
- Inflanted surrounding structure such as tendons, bursa etc.

Deformity

Deformity is the sign of chronic, destructive arthritis. It ranges from mild changes to gross destruction of joint.

- *Subluxation* is said to be present when displaced parts of the joint surfaces remain partially in contact.
- *Dislocation* means displacement where there is loss of contact between joint surfaces.

Muscle wasting

Muscle wasting around the joint results from disuse of the joint, inflammation of the surrounding tissues and sometimes due to nerve entrapment.

FEEL (PALPATION)

While palpating the joint watch the patient's face, be gentle, start palpation where the joint is least likely to be tender. Feel the following features:

Warmth

Warmth is a feature of inflammatory joint disease such as RA, septic arthritis, and gout.

Tenderness

It is a guide to acuteness of the inflammation. There may be 4 grades of tenderness as following:

1. Patient complains of pain on palpation.
2. Patient complains of pain on palpation and winces.
3. Patient complains of pain on palpation, wines and withdraws the joint.
4. Patient does not allow palpation.

Swelling

Determine limits of swelling and feel for three types of swellings:

- *Soft spongy swelling:* it results from synovitis.
- *Soft fluctuant swelling:* it results from effusion, usually in large joints.
- *Hard bony swelling:* it is hard and immobile and develops due to osteophyte formation or subchondral bone thickening.

MOVE (PASSIVE MOVEMENT)

- Joint must be put through a full range of movement. Joint movement may be active performed by the patient or passive performed by the examiner.
- Limitation of passive movement indicates something wrong in or around the joint and it is more specific to joint problem as compared to the active movement.
- Movement must be attempted gently and it will be restricted if the joint is painful, having tense effusion or fixed deformity. The joint may have limited extension (called fixed flexion deformity) or limited flexion (called fixed extension deformity).
- Instability of joint that is characterized by abnormal movement is usually due to weak surrounding ligaments. It is tested by attempting to move the joint gently in abnormal direction.
- Joint crepitus is a grating sensation or noise from the joint and indicates irregularity of the articular surface.

ARTHRITIS

Main causes of arthritis

1. Rheumatoid arthritis
2. Osteoarthritis
3. Connective tissue disorders
   - Systemic lupus erythematous
   - Polymyositis / dermatomysitis
   - Systemic sclerosis
4. Polymyalgia rheumatica
5. Crystal deposition diseases
   - Gout
   - Pyrophoshate arthropathy
6. Infective arthritis
7. Reactive arthritis
8. Ankylosing spondylitis
9. Juvenile arthritis. E.g. Still's disease
10. Psoriatic arthritis.

RHEUMATOID ARTHRITIS (RA)

Rheumatoid arthritis is a chronic symmetrical polyarthritis of unknown cause and is characterized by chronic inflammatory synovitis of mainly peripheral joints along with systemic disturbances and extra-articular features. Course of disease is prolonged with exacerbations and remissions.

Characterized by:

- Symmetrical inflammatory polyarthritis
- Extra-articular involvement e.g. in the lungs and many other organs.
- Progressive joint damage causing severe disability.

INCIDENCE

- Prevalence 1-1.5%
- Female to male ratio 3:1
- Peak age incidence between 20-40 years.

ETIOLOGY

The cause of rheumatoid arthritis (RA) is unknown. Following may be the risk factors:

1. Genetic factors may be involved because it is usually associated with HLA- DR4 in whites and DR1 in Indo-Pak.

2. Autoimmunity: RA is considered to be an autoimmune disease for the following reasons:
   - Autoantibodies are present.
   - Immune complexes are common in synovial-fluid and the circulation.
   - There is defect in cell-mediated immunity.

3. Female gender is a risk factor and this susceptibility is increased post-partum and by breast feeding.
4. Cigarette smoking is also a risk factor.

PATHOGENESIS

RA is a disease of the synovium. There are two main pathological characteristics:

- Inflammation
- Proliferation

The synovium shows signs of chronic inflammation. There is swelling and congestion of the synovial membrane and the underlying connective tissue which become infiltrated with lymphocytes, plasma cells and macrophages. Effusion of synovial fluid into the joint space takes place during active phases of the disease.

The synovial membrane then proliferates and grows out over the surface of the cartilage, which causes erosion and destruction of the cartilage.

CLINICAL FEATURES

RA usually presents with insidious onset of pain and stiffness in the small joints of hands and feet which eventually lead to bilateral symmetrical peripheral polyarthritis. In 25% cases it presents as monoarthritis such as involvement of only knee joint.

TYPICAL PRESENTATIONS OF RA

Classical (chronic persistent): Majority of patients present insidiously with fatigue, generalized weakness and vague musculoskeletal symptoms for weeks or months and then pain, stiffness and swelling of small joints of hands and wrists. The disease follows the remitting and relapsing course over many years. It may be seropositive or negative for rheumatoid factor. Seropositive patients develops more joint damage as compared to seronegatives.

Acute: About 10-15% patients present with a rapid onset over a few days or overnight with a severe symmetrical polyarticular involvement, often accompanied by constitutional symptoms e.g. fever, lymphadenopathay and splenomegaly.

Palindromic: A few patients present with recurrent acute episodes of joint pain and stiffness usually of single joint lasting only a few hours or days followed by rapid return to normal. In 1/3 of such cases the disease evolves into one or more typical of arthritis.

Transient
A self- limiting disease lasting less than 12 months and leaving no permanent joint damage. It is usually seronegative for IgM rheumatoid factor.

Remitting
There is a period of several years during which the arthritis is active but then remits, leaving minimal damage.

Rapidly progressive
The disease progresses rapidly over a few years and leads to joint damage and disability. It is usually seropositive and has high incidence of systemic complications.

PATTERNS OF ONSET IN RHEUMATOID ARTHRITIS
- Insidious 70%
- Acute 15%
- Oligoarticular 45%
- Polyarticular 35%
- Systemic 10%
- Monoarticular 20%
- Palindromic 5%

SYMPTOMS

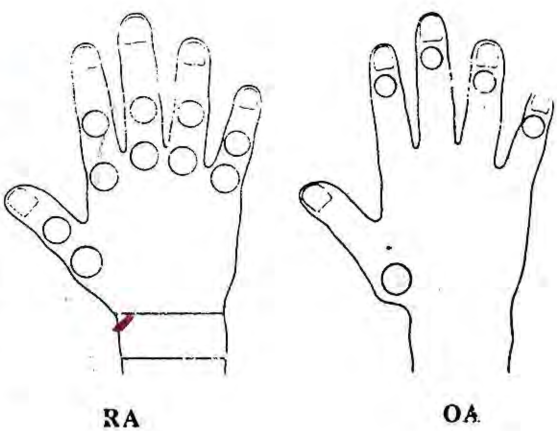
- **Joint pain:** The pain is worst on waking in the morning and improves progressively with activity. There is often pain at night disturbing the sleep.
- **Morning stiffness:** Often lasting for several hours and then subsides. Its duration is a useful indicator of activity of disease. It is characteristic of inflammatory joint disease.
- **General symptoms**: Fatigue and malaise.
- **Extra-articular symptoms:** discussed below

SIGNS

- **Swelling:** soft swelling caused by effusion or synovial proliferation.
- **Warmth**
- **Tenderness** on pressure or movement.
- **Limitation of movement** with muscle wasting around affected joints.
- **Deformities** occurring in the later stages of the disease.
- **Subcutaneous nodules** (in 20%) mostly situated over bony prominence
- **Extra-articular features.**

Pattern of joint involvement
Although any joint may be affected in R.A, the proximal interphalangeal and metacaropohalangeal joints of fingers as well as the wrist, knee ankles and toes are most often involved. Distal interhalangeal joints are characteristically spared.

D/D from osteoarthritis
- In osteoarthritis, the number of joints affected is much less than RA.
- In RA distal interphalangeal joint is spared while in osteoarthritis (OA) it is characteristically involved.
- The joints most commonly involved in OA are weight bearing joints e.g. knee and hip joints.

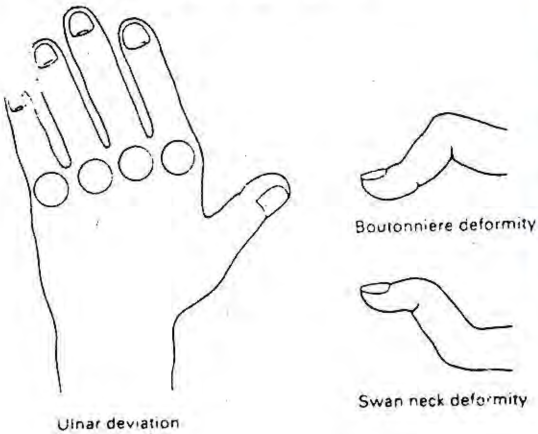


DEFORMITIES

As the disease advances (after months or years) pain, muscle spasm and joint destruction result in limitation of joint movement, joint instability, subluxation (partially dislocation) and deformities.

The hands and wrists

- *Spindling of the fingers:* In early stages, swelling of the metacarpophalangeal joints produces spindling of the finger.
- *Swan neck deformity:* Characterized by hyperextension at the proximal interphalangeal joints and fixed flexion at the distal interphalangeal joints.
- *Button hole deformity:* Characterized by fixed flexion of the proximal interphalangeal joint and extension of the distal interphalangeal joint.
- *Z deformity of the thumb:* characterized by hyperextension of the first interphalangeal joint and flexion of the first metacarpophalangeal joint with a consequent loss of thumb mobility.
- *Carpal tunnel syndrome:* Tenosynovitis at the wrist can entrap the median nerve and produce carpal tunnel syndrome.
- *Extra – articular features* in hands may be palmer erythema, and vasculitic lesions in nail beds, nail folds, and digital pulp.



Characteristic hand deformities in rheumatoid arthritis.

The feet and ankles.

Lateral deviation of the toes and subluxation (partially dislocation) of the metatarsophalangeal joints, so that the heads of the metatarsals become palpable in the soles of the feet and patient often describes as sensation of walking on pebbles. Ankle develops valgus deformity.

The knee

- Synovial effusions and quadriceps wasting are early features.
- Later on flexion, *valgus* (bent outward) or *varus* (bent inward) deformities appear with joint instability.
- Synovial effusion (demonstrated with patellar tap by fixing the knee with the fingers and thumb of left hand, then sharply tapping the patella downwards produces a dip when effusion is resent).

Baker's cyst: It is an extension of inflamed synovium into the popliteal space, causing pain and swelling. High pressure generated by flexion of knee can cause rupture of cyst into the calf, manifesting as calf swelling, tenderness and pitting edema.

Cervical spine

Synovitis of upper cervical spines leads to bone destruction, damage of ligaments that causes *atlantoaxial subluxation* which may damage the spinal cord.

COMPLICATIONS OF RHEUMATOID ARTHRITIS

- Ruptured tendons
- Ruptured Baker's cyst
- Joint infection
- Spinal cord compression
- Amyloidosis presenting as nephrotic syndrome
- Complications of drug therapy

REVIEW OF CLINICAL FEATURES OF RA

Symptoms

- Joint pain, Morning stiffness
- Extra-articular symptoms

Signs

- Swelling, warmth, tenderness of joints
- Limitation of movement of joints
- Deformities
- Subcutaneous nodules and other extra-articular features

Pattern of joint involvement

- Proximal interphalangeal & metacarpophalangeal joints of fingers.
- Wrist, knee ankle and toe.
- Distal interphalangeal joint spread.

Deformities

Hands:

- Spindling of fingers.
- Subluxation of metacarpophalangeal joints
- Swan neck deformity
- Buttonhole deformity
- Z-deformity of thumb
- Carpal tunnel syndrome

Feet

- Lateral deviation of the toes
- Subluxation of the metacarpophalangeal joints.

Knee

- Synovial effusion
- Valgus & varus deformities

Cervical spine

- Atlantoaxial subluxation.

EXTRA - ARTICULAR FEATURES

1. Musculoskeletal

- *Subcutaneous modules: (in 20%):* usually seen at sites of pressure or friction such as the extensor surfaces of the forearms below the elbow, scalp, sacrum, scapula, Aschilies tendon, as well as on the fingers and toes.
- *Bursitis:* The olecranon and other bursae may become swollen.
- *Tenosynoyitis:* Particularly affecting the flexor tendons in the palm of the hand and may contribute to flexion deformities.
- *Muscle wasting*: around affected joints especially in the hands.

2. Neurological

- *Carpal tunnel syndrome* (More common nervous involvement).
- *Atlanto-axial subluxation:* Most serious neurological abnormality causing cervical cord compression. Death can occur during intubation or endoscopy.
- *Polyneuropathy* causing glove and stocking type sensory loss mostly involving the legs.
- *Mononeuritis multiplex.*

3. Ocular

- *Sjogren's Syndrome:* Commonest eye problem rheumatoid arthritis.
- *Scleritis* – causing painful red eye
- *Keratoconjunctivitis*

5. Hematological

- *Thrombocytosis*
- *Eosinophilia*
- *Anemia* is always present. It may be
  - Normocytic normochromic due to chronic disease.
  - Iron deficiency – due to GIT blood loss from analgesic ingestion.
  - Hemolytic) + ve Coomb's test).

6. Pulmonary

- Pleural effusion (commonest lung problem)
- Diffuse fibrosing alveolitis (rare)
- Rheumatoid nodules in the lungs
- <u>*Caplan's Syndrome*</u>: occurrence of nodular pulmonary fibrosis in patients with RA exposed to various industrial dusts.

7. Cardiac

- Pericardial rub often heard
- Pericarditis, myocarditis
- Conduction defects (heart block)
- Aortitis

8. Lymphatic

- Lymphadenopathy – in the distribution of affected joints.
- Splenomegaly
- *Felty's syndrome:* Comprising rheumatoid arthritis, splenomegaly with neutropenia.

9. Skin

- Vasculitis: Causing nail fold lesion in hands
- Leg ulcers: In patients with Felty's syndrome.

11. Systemic

- Fever
- Weight loss
- Susceptibility to infection

EXAMINATION OF PATIENT WITH RHEUMATOID ARTHRITIS

General inspiration
Look for Cushingoid appearance due to steroid use.

Hands
Put the hands on a pillow, examine first dorsum of hand and then palm and look for:

- Symmetrical small joint polyartheritis.
- Ulnar deviation.
- Swan neck, boutonniere deformity, and Z deformity of thumb.
- Finger nails for vasculitic change.
- Wasting of small muscles of hand.
- Look at palm for palmar erythema
- Signs of carpal tunnel syndrome.

Wrist
Look for synovial thickening and test for carpal tunnel *(Tinel" sign).*

Elbow
Rheumatoid nodules

Eyes

- Redness and dryness (Sjogren's syndrome) occurring in 10-15% of cases.
- Scleritis (white or purple-red nodule surrounded by intense redness) occurs in 1% of cases and often bilateral.
- Cataract due to steroid use
- Anemia due to iron deficiency.

Mouth and parotid
Dry mouth and enlarged parotid due to Sjogren's syndrome.

Neck

- Examine cervical sine for tenderness.
- Reduction of rotation movement.
- Examine for lymphadenopathy.

Chest
Examine lungs for pleural effusion or pulmonary fibrosis. Caplan's syndrome is the presence of rheumatoid lung nodules in combination with pneumococoniosis.

Abdomen
Splenomegaly (in 10% cases)
Epigastric tenderness (due to NSAIDs induced peptic ulcer)

Lower limbs

- Note quadriceps wasting, knee joint effusion, flexion contractures.
- Backer's cyst in popliteal fossa.
- Peripheral neuropathy in stocking distribution.
- Look for signs of spinal cord compression due to dislocation of first cervical vertebra.

INVESTIGATIONS

No test is specific for diagnosis of rheumatoid arthritis. Following investigations may be helpful.

RA FACTOR

Rheumatoid factor (RA factor) is autoantibody against Fc fragment of 1gG & is present in about 70% of cases. Presence of RA factor does not establish the diagnosis of RA but it can be of prognostic significance because patients with high RA titer tend to have more severe and progressive disease with extra- articular manifestations. This test can be employed to confirm a diagnosis in individuals with a suggestive clinical presentation and if present in higher titer, to designate patients at higher risk for severe systemic disease. RA factor is positive in 10% of normal population.

DISEASE WHICH MAY BE ASSOCIATED WITH POSITIVE RA FACTOR

Diseases involving joints
- Sjogren's syndrome (905)
- Rheumatoid arthritis (70%)
- Systemic lupus erythematous (50%)
- Systemic sclerosis (30%)
- Polymyositis / dermatomyositis (50%)
- Mixed connective tissue disease.

Chronic infections (low titres)
- Tuberculosis
- Leprosy
- Infective endocarditis
- Kalaazar

Normal population
- Elderly
- Relatives of patients with rheumatoid arthritis

Miscellaneous
- Autoimmune chronic active hepatitis
- Fibrosing alveolitis.

ANA:

Antinuclear antibody is positive in 30% of cases.

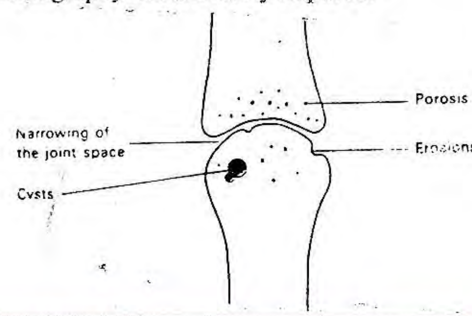
BLOOD CP/ESR

- Anemia
- Thrombocytosis in proportion to the severity of joint inflammation.
- WBC may be normal, high or low (in Felty's syndrome).
- ESR and C-reactive protein (CRP) are raised in proportion to the activity of the inflammatory process (inflammatory markers).

RADIOGRAPHY

X-rays taken during first 6 months are read normal. Early changes occur in the wrist or feet and consist of:

- Symmetric involvement, juxtra-articular *osteopenia* (if may become apparent within weeks of onset).
- Later loss of articular cartilage and *bone erosions* develops after months of sustained disease activity. Bone erosion is the hallmark of inflammatory arthropathy.
- MRI and bone scan detect early inflammatory changes that are not apparent from standard radiography but are rarely required.



STAGES OF X-RAY PROGRESSION IN REHEUMATOID ARTHRITIS

- I Periarticular osteoporosis (osteopenia)
- II Loss of articular cartilage ("joint space")
- III Bony erosions (especially on margins)
- IV Subluxation and Ankylosis

EXAMINATION OF JOINT FLUID

Measures	Normal	Non-inflammatory e.g. osteoarthritis	Inflammatory e.g. rheumatoid arthritis	Purulent e.g. septic arthritis
Volume (ml) knee	< 3.5	Often >3.5	Often >3.5	Often >3.5
Clarity	Transparent	Transparent	Translucent to opaque	Opaque
Color	Clear	Yellow	Yellow to opalescent	Yellow to green
WBC (per μL)	<200	200-300	3000-50,000	>50,000
Polymorphs (neutrophils)	<25%	<25%	50% or more	75% or more
Culture	Negative	Negative	Negative	Usually positive
Glucose (mg/dL)	Nearly equal to serum	Nearly equal to serum	> 25, lower than serum	< 25, much lower than serum

SYNOVIAL FLUID ASPIRATION

The fluid is usually turbid, with reduced viscosity, increased protein content and a slightly decreased or normal glucose concentration. WBC count varies b/w 5-50,000 cells/μL with polymorph predominant. Complement C3 and C4 are markedly low.

DIAGNOSIS

Diagnosis of RA is based on history, examination, x-ray findings and serology (RA factor). Rheumatoid arthritis presents initially with non-specific symptoms but assumes its characteristic features with in 1-2 years of onset. The following features support diagnosis of rheumatoid arthritis:

- Bilateral symmetrical inflammatory polyarthritis involving small and large joints in both the upper and lower extremities with sparing of axial skeleton except cervical spine suggest the diagnosis.
- Systemic features indicative of inflammatory nature of the disease such as morning stiffness support the diagnosis.
- Presence of subcutaneous nodules is a helpful diagnostic features.

MARKERS OF ACTIVE INFLAMMATORY DISEASE

- Anemia of chronic disease
- Thrombocytosis
- Raised acute phase proteins (e.g. C-reactive protein).
- Raised plasma viscosity.
- Raised erythrocyte sedimentation rate (ESR)

CRITERIA FOR THE DIAGNOSIS OF RHEUMATOID ARTHRITIS
(American Rheumatism Association 1988 Revised criteria)

1. Morning stiffness (> 1 hour).
2. Arthritis of 3 or more joint areas.
3. Arthritis of hand joints.
4. Symmetrical arthritis
5. Rheumatoid nodules
6. rheumatoid factor
7. Radiological changes

- Duration of six weeks or more
- Diagnosis of RA made with 4 or more criteria.

DIFFERENTIAL DIAGNOSIS

Rheumatoid arthritis in initial phase is not a straight forward diagnosis, other conditions have similar presentation and they should be ruled out.

Rheumatic fever

- Migratory arthritis
- Raised ASO titer
- Dramatic response to aspirin
- Carditis and erythema marginatum may occur in adults but chorea and subcutaneous nodules virtually never do.

SLE

- Butterfly rash
- Discoid rash.
- Photosensitivity
- Alopecia
- Higher titer to anti-DNA
- Renal involvement (e.g. proteinuria).
- CNS involvement.

Osteoarthritis

- No systemic features.
- Joint pain is characteristically relieved by rest while the pain of RA is increased by inactivity.
- Morning stiffness is much less and for short period.
- In contrast to RA, it spares wrist and metacarophalangeal joints and commonly involves distal interphalangeal joints to produce Heberden nodes especially in women.
- Joint swelling is hard due to bony hypertrophy. Slight effusion may be present particularly in the knee, while in RA joint swelling is soft due to effusion and synovial thickening.
- It mostly involves weight bearing joints e.g. spine, hip, and knee.

Gouty arthritis

- Intermittent and monoarticular in early years, later it may become polyarticular that mimics RA. Gouty tophi can resemble rheumatoid nodules.
- Early history of intermittent monoarthritis and the presence of synovial urate crystals are distinctive features of gout.

Septic arthritis

- Sudden onset of acute arthritis usually monoarticular and most often are weight bearing joints and wrists.
- Fever & chills.
- Frequent presence of primary focus of infection elsewhere e.g. gonococcal infection, infective endocarditis. I/V drug abuse.
- Joint effusion are large, with WBC count more than 50000/μL.
- Gram stain and culture are mostly positive.
- Response to appropriate antibiotics.

Other D/D are polymyalgia rheumatica, seronegative arthritis, postviral arthritis e.g. hepatitis B & hypertrophic pulmonary osteoarthropathy.

MANAGEMENTS

There are five stages in the management of rheumatoid arthritis.

NON-PHARMACOLOGICAL TREATMENT

Rest

Rest ameliorates symptoms. Complete bed rest for patients with profound systemic and articular inflammation. With mild inflammation, 2 hours of articular rest decreases joint inflammation.

Exercise

Exercises are designed to preserve joint motion, muscular strength and endurance. Initially passive range of motion is best tolerated. As tolerance for exercise increases and the activity of the disease subsides, progressive resistance exercises may be introduced. Patients are particularly at risk of developing progressive joint stiffness and deformity, therefore they should undertake simple exercise to maintain joint mobility and muscle power.

Heat and cold

Heat and cold have muscle relaxing and analgesic effects. Patient may derive relief from hot bath or local application of cold.

Splits

Splints may provide joint rest, reduce pain and prevent contractors. They should be applied for short period.

Weight loss
Weight loss is also beneficial especially to reduce symptoms of weight bearing joints.

PHARMACOLOGICAL TREATMENT

Medical management of RA involves 4 general approaches.

1. Non-steroidal ant-inflammatory drugs (NSAIDs)
2. Low dose corticosteroids.
3. Disease Modifying Anti-Rheumatic Drugs (DMARDs).
4. Immunosuppressive drugs.

Non - steroidal anti-inflammatory drugs (NSAIDs)

Non-steroidal anti-inflammatory drugs have analgesic and anti-inflammatory effect and therefore they are used to control signs and symptoms of the local inflammatory process. They are not capable of preventing erosions or altering progression of the disease.

> NSAIDs relieve pain by inhibiting cyclooxygenase (COX), the enzyme that converts arachidonic acid to prostaglandins. Although prostaglandins play an important role in promoting inflammation and pain they also help in protection of gastric mucosa.
> There are two types of cyclooxygenase (COX).
> - COX-1: it gives protection to gastric mucosa.
> - COS-2: it is produced in inflammatory tissues.
>
> Therefore, selective inhibition of COX-2 will reduce inflammatory process without causing gastric ulcer. Celecoxib is a selective COX-2 inhibitor. Its efficacy is similar to other NSAIDs with less likely gastric ulceration.
>
> Another approach to reducing the GI side effects of NSAIDs is to add either Omeprazole 20 mg daily or Famotidine 40 mg BID or Misoprostol 200μg BID. Antacids and Ranitidine either do not work or do not as work as omeprazole in prevention of NSAID induced GI side effects.

Side effects of NSAIDs

- Gastric ulceration and GI hemorrhage.
- Renal toxicity such as interstitial nephritis, nephrotic syndrome, reversible renal failure and aggravation of baseline hypertension. Whether (COX 2 inhibitor has less renal toxicity than traditional NSAIDs, is not yet established.
- All NSAIDs except Celecoxib interfere platelet function and prolong bleeding time. This effect is reversible when NSAIDs are stopped except aspirin that irreversibly inhibits platelet function, so the bleeding time is prolonged until new platelets are formed that takes 7-10 days when aspirin is given.

Criteria for selection of NSAIDs is

- Low incidence of side effects.
- Good safety margin
- Convenient dosage schedule.

Simple analgesics
These drugs having only analgesics effects but no appreciable anti-inflammatory action, can be used in combination of NSAIDs when pain relief is inadequate e.g. paracetamol (peripheral acting) and dextropropoxyphene (Distalgesic)—central acting.

Commonly used NSAIDs

Generic names	*Proprietary names*
Diclofenac sodium	Voltral
Diclofenac potassium	Caflam
Piroxicam	Feldene
Mefenamic acid	Ponstan
Ibuprofen	Brufen
Naproxin	Synflex
Nabumetone	Relifex
Tenoxicam	Tilcotil

Corticosteroids

Corticosteroids usually produce an immediate and dramatic anti-inflammatory affect in RA. They can be used on short-term basis for the following *indications:*

- Severe exacerbations which are not remitting with NSAIDs and disease modifying drugs.
- Severe extra- articular manifestations e.g. pericarditis, perforating eye lesions.
- Active and progressive disease that does not respond favorably to conservative management.
- When there is contraindication to or therapeutic failure of methotrexate or other disease modifying drugs.
- When other measures fail to control persistently disabling symptoms in breadwinners, young mothers who have to return to work.

- Low dose (< 7.5 mg/day) is effective to achieve desired clinical effect.
- Recent evidence suggests that low dose corticosterid therapy may retard the progression of bone erosions.
- Intra-articular corticosteroid may be helpful if one or two joints are the chief source of difficulty. Inj. Triamcinolone 10-20 mg depending on size of the joint may be given for symptom relief, but no more than 4-times years.

Disease modifying anti – rheumatic drug

Disease Modifying Anti-Rheumatic Drugs (DMARD) have property to modify the destructive capacity of the disease. They include methotrexate, antimalarial, sufasalazine, penicillamine, azathioprine, cyclophosphamide and gold.

DMARD should be added early and used aggressively to maximize the chance of achieving a good outcome. The appearance of benefit from this therapy is usually delayed for weeks or months. Six months of uninterrupted treatment with a disease modifying drug is usually required to assess its efficacy. They augment the response to concomitantly used NSAIDs or corticosteroids given in low doses. In addition to clinical improvement, there is frequently an improvement in serologic evidence of disease activity e.g. titer of RA factor; ESR and C-reactive protein are declined.

Patients receiving one of the DMARD will take it, on average for 3-5 years before the lack of efficacy or toxicity forces discontinuation of its use. A second disease-modifying agent is substituted for the first one when there is therapeutic failure or toxicity develops. Failure to response to one agent does not predict a negative response or intolerance to the others.

Indications

- Persistent symptoms and signs of inflammatory arthritis.
- Evidence of progressive radiological damage.
- Troublesome extra-articular manifestations
- Palindromic rheumatoid arthritis.

Methotrexate

Methotrexate is the treatment of choice. It is generally well tolerated and often produces beneficial effect in 2-6 weeks compared with 2-6 months onset of action for other drugs such as antimalarials). Maximum improvement is observed after 6 months of therapy, with little additional improvement thereafter.

Dosage

- Tab. Methotrexate 2.5 mg 3 tablets (7.5mg) orally once a week.
- If the patient has tolerated methotrexate but has not responded in one month, the dose can be increased to 15mg (6 tablets) orally once a week.
- The maximum dose is 20mg per week.

Side effects

- Gastric irritation and stomatitis (most common).
- Interstitial pneumonitis (rare).
- Cirrhosis of liver (very rare) therefore contraindicated in chronic hepatitis.
- Bone marrow suppression that predisposes to infection.
- Concomitant administration of *folic acid* may diminish the frequency of some side effects.

Antimalarials

- Used for mild cases
- About 20-25% patients respond
- Onset of action takes 2-6 months. Drug should be discontinued if there is no effect within 6 months.
- Although they are less effective than other DMARDs they have less side effects and better patient compliance.

Dosage

Hydroxychloroquine sulfate 200-400mg daily

Side effects

- Nausea, diarrhea, rash, ototoxicity
- Neuropathy, myopathy
- *Pigmentary retinitis* causing blindness may occur after more than a year therapy.

- *Corneal opacities* due to drug accumulation can occur which disappear when drug is withdrawn. Therefore, ocular examination is required every 6-12 months. In order to reduce the risk of ocular toxicity antimalarials are often given for only 10 months in each year (with 2 months gap)

Sulphasalazine (Salazopyrin)

- It is frequently used DMARD.
- About 50% patients respond in 3-6 months.

Side effects

- Nausea, vomiting (common).
- Neutropenia and thrombocytopenia (in 10-25%), and therefore requires blood CP every 2-4 weeks for first 3 months, then every 3 months.
- Hemolysis in G6PD deficiency patients.

Dosage

Sulhasalazine (Tab. Salazopyrin 500mg) twice daily, increase 500mg/week until the patient improves or the daily dose reaches to 3 gram (i.e. 6 tablets).

D-Penicillamine

D-Penicillamine may be used in patients with severe rheumatoid arthritis who have continuing active disease in spite of therapy with methotrexate.

Clinical effect is noted several weeks after a effective dose, maximum effect after 4-6 months.

Dosage

D-Penicillamine (Tab. Vistamin 250mg) is commenced in a single evening dose and dosage is increased by no more than 250 mg monthly to maximum 1 g daily.

Side effects

- Oral ulcers, loss of taste, rash, thrombocytopenia, fever, leukopenia and aplastic anemia. (up to 50% patients develop some of the above side effects).
- Proteinuria and nephrotic syndrome may occur.
- Monitor blood CP and urine D/R.

Gold salts

- Gold salts are indicated for patients who fail to improve on or who cannot tolerate methotrexate. About 60% of patients respond to gold therapy.
- They can be given orally or I/M injection.
- Side effects are rash, exfoliative dermatitis, mouth ulcers, enterocolitis, proteinuria, nephrotic syndrome and aplastic anemia.
- Monitor blood count and urine analysis.

Immunosupressive therapy

These drugs are used in patients who have clearly failed therapy with DMARDs. Immunosupressive drugs are as effective as DMARDs but are more toxic.They include azathioprine. Cyclophoshamide, chlorambucil and cyclosporin-A. Methotrexate is also immunosuppressive drug but included in DMARDs.

Indications

- Life threatening extra-articular manifestation which have failed to respond to corticosteroids or DMARDs.
- Severe active symptomatic and progressive joint disease that has failed to respond to all other forms of therapy.
- Patients receiving unacceptably high doses of corticosteroids in whom dose reduction has not been possible.

Azathioprine (Tab. Imuran 25mg)

- Initial dose is 1 mg/kg, gradually increased to maximum of 2.5-3 mg/kg.
- Side effects are vomiting, diarrhea, stomatitis, hepatitis, home marrow suppression and susceptibility to infection.

Cyclophosphamide

- Dosage 1-2 mg/kg.
- Side effects are alopecia, azoospermia, bone marrow suppression and teratogenesis.

Cyclosporin A

- Dosage 2.5-4mg/kg
- Side effects are nausea, hepatotoxicity, hypertension and renal impairment.

COMBINATION THERAPY

- Combination therapy can be considered for patients who failed to respond individual agent.
- The combination of methotrexate chloroquine and sulphasalazine is more effective than methotrexate alone.
- The combination of cyclosporin and methotrexate is more effective than methotrexate alone.

NEWER THERAPY

Tumor necrotic factor (TNF) inhibitor:
It combines with circulating TNF which is one of the major cytokines responsible for inflammation in rheumatoid arthritis Etanercept, injected as 25 mg twice weekly show good short-term efficacy and safety for reduction of inflammation. Side effect is local irritation at the site of injection. It is as expensive drug.

Interleukins (IL-I & IL-6) receptor blocker.
It has been shown to have rapid anti-inflammatory effect.

FOLLOWUP

- Ask the patient for severity of joint pain, duration of morning stiffness, fever, fatigue and weight loss.
- Look for joint swelling deformities distribution of involved joints and wasting of muscle around the joint. Feel for warmth & tenderness. Move to assess range of passive movement & muscle power.
- Examine for extra-articular manifestation.
- Make sure that the patient is taking medicines in proper dosage and assess for the side-effects.

PROGNOSIS

The course and prognosis in RA are very variable. After 10 years the disease pattern is as following.

- Complete remission in 25%.
- Moderate impairment in 40%
- Severe disability in 25%
- Severely crippled 10%.

Poor prognostic factors

- High titers of rheumatoid factor
- Insidious onset of disease.
- More than a year of active disease without remission.
- Early development of modules or erosin
- Extra – articular manifestations.
- Severe functional impairment.

SURGICAL PROCEDURES IN RA AND OA.

Soft tissue release (decompression)

- Carpal tunnel syndrome due to median nerve compression
- Tarsal tunnel syndrome due to posterior tibial nerve entrapment
- Flexor tendon (for relief of trigger fingers)

Tendon repairs and transfers

- Extensor tendons of hands for rupture of extensor tendons
- Flexor tendon of thumbs and fingers for rupture of flexor tendons

Synovectomy

- Wrist and extensor tendon sheaths and excision of ulnar styloid for pain relief and prevention of extensor tendon rupture.

Osteotomy

- Kellar's operation
- Femoral osteotomy
- Tibal osteotomy

Excision arthroplasty

- Radial head
- Lateral end of clavicle

Joint replacement

Hip, knee, elbow, shoulder, ankle, metacarpophalangeal joints of hands.

Arthrodesis

- Interhalangeal joint of thumb or fingers
- Metacarpophalangeal joint of thumb
- Wrist
- Ankle and subtalar joints

FELTY'S SYNDROME

Felty's syndrome is the association of splenomegaly and neutropenia with rheumatoid arthritis involving < 1% of RA patients.

- Age of onset 50-70
- F > M
- Incidence < 1% RA patients
- Long-standing RA
- Deforming but inactive disease
- Seropositive

Common clinical features

- Splenomegaly
- Lymphadenopathy
- Weight loss
- Skin pigmentation
- Keratoconjunctivitis sicca
- Nodules
- Vasculitis
- Leg ulcers
- Recurrent infections.

Laboratory findings

- Anemia
- Neutropenia
- Thrombocytopenia
- Impaired T and B cell immunity
- Abnormal liver function.

OSTEOARTHRITIS

Osteoarthritis or degenerative bone disease is the end-result of variety of patterns of joint failure, and is characterized by degeneration of articular cartilage and stimultaneous proliferation of new bone, cartilage and connective tissue. Its greatest impact is on weight-bearing joints e.g. hips and knees. There are no extra-articular features and no systemic illness.

ETIOLOGY

Primary: when etiology unknown

Secondary: when degenerative joint changes occur in response to a recognizable local or systemic factor.

CUASES OF SECONDARY OSTEOARTHRITIS

Developmental Hip dysplasia	**Endocrine** Acromegaly
Traumatic • Intra-articular fracture • Meniscectomy • Occupational • Ehlers-Danlos syndrome	**Inflammatory** • Rheumatoid arthritis • Gout • Septic arthritis • Hemophilia
Metabolic • Alkaptonuria • Hemochrmatosis • Wilson's disease • Chondrocalcinosis	**Aseptic necrosis** • Corticosteroid use • Sickle cell disease • SLE
Neuropathis • Tabes dorsalis • Syringomyelia • Diabetes mellitus • Peripheral nerve lesions	**Miscellanous** • Paget's disease • Gaucher's disease

PATHOGENESIS

Osteoarthritis is a disease of cartilage. Different stimuli can start the degenerative process but the two most obvious are:

- Mechanical insults i.e. trauma
- Biochemical abnormalities of cartilage (the chondrocytes in cartilage are believed to initiate the deterioration by releasing enzymes that degrade collagen and protoglycan. Break in the collagen fibers allow the uptake of water, as a result cartilage swells and splits.

PATHOLOGY

- Progressive cartilage loss until hard bone is all that remains.
- Synovial membrane heavily infiltrated with mononuclear cells.
- Thickening of subchondral bone with cyst formation.

PATTERN OF JOINT INVOLVEMENT

Nodal osteoarthritis:
Nodal osteoarthritis occurs predominantly in middle – aged women presenting with bony swelling of distal interphalangeal joint Heberden's nodes), swelling of proximal interphalangeal joint (Bouchard's nodes). The onset may be acute with severe pain, swelling and inflammation.

Non-nodal osteoarthritis:
It is less prominent in distal interphalangeal joint.

Erosive osteoarthritis:
It is severe osteoarthritis presenting with episodic signs and symptoms of joint inflammation with development of destructive subchondral erosions in proximal and distal itnerphalangeal joints.

Osteoarthritis of knees
It is often associated with obesity and is more common in women.

CLINICAL FEATURES

The joints most frequently involved are those of spine, hips, knees and hands. The disease is confined in one or only a few joints in the majority of patients.

Symptoms

Pain

- Typically in the knees, hip, hands.
- Worst in the evening.
- Aggravated by use and relieved by rest.
- Intermittent at first but later chronic.

Morning stiffness:
Usually lasting up to half an hour, stiffness also after sitting.

Disability:
Movement in the affected joints becomes increasingly limited, initially as a result of pain and muscular spasm, but later because of capsular fibrosis, osteophyte formation and remodeling of bone.

Signs

- *Joint swelling:* Characteristically hard and bony sometimes with associated effusion.
- *Crepitus*: On movement may be felt or even heard.
- *Muscle wasting:* Wasting of the muscles around the affected joints.
- *Joint deformities*: Particularly in knee joint. Valgus (outward) or varus (inwards) or flexion deformities are seen with instability of the joint due to absence of normal muscular control as a result of muscle wasting.

Hands

Heberden's nodes: These are bony swelling at the distal interphalangeal joints of the fingers and *Bouchard's nodes* at the proximal interphalangeal joints.
At first the joints are often red, warm, swollen and very tender (hot-Heberden nodes), later the inflammation disappear leaving knobby but often painless swelling.



Nodal osteoarthritis. Distal interphalangeal joint subluxation with Heberden's nodes. There are also early Bouchard's nodes at the proximal interphalangeal joints.

Feet:

The metatarsophalangeal joint is often affected, sometimes called "poor man's gout".

DIFFERENTIAL DIAGNOSIS

Osteoarthritis

- Distal interphalangeal joint involvement
- Number of joints involved is less.

Rheumatoid arthritis

- Proximal interphalangeal metacarophalangeal joints involvement
- Number of joints involved is more.

INVESTIGATION

X-ray

- Narrowing of the joint space: due to loss of the cartilage.
- Formation of osteophytes at the margin of the joints.
- Sclerosis of the underlying bone.
- Cyst formation.

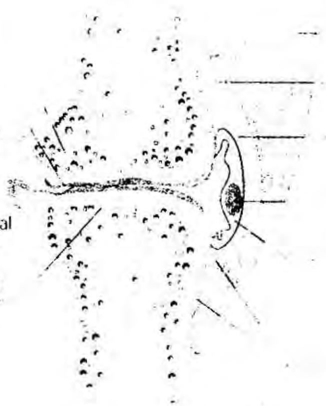


Diagram and X-ray of [illegible] osteoarthritis

Blood test

Blood count & ESR are characteristically normal.

Synovial fluid:

Synovial fluid is viscous and has a low cell count.

MANAGEMENT

General measures

- Weight loss in obese patient
- Rest and avoidance of undue trauma and physical stress.
- Suitable walking stick.
- Change in occupation to lighter work.

Drug treatment

There is no drug to reverse the pathological changes. For the symptomatic relief non-steroidal anti-inflammatory drugs (NSAIDs) can be used. Intra-articular corticosteroids can be used for inflammatory exacerbations. Injections should be preceded by aspiration of any fluid in the joint.

Physical therapy

- Application of heat may give some relief
- Proper exercises are useful to maintain muscle power.
- Hydrotherapy for osteoarthritis of hip.

Surgery

Joint replacement and other surgical procedures discussed in the section of rheumatoid arthritis.

INFECTIVE ARTHRITIS

SEPTIC ARTHRITIS

(Non-gonococcal acute bacterial arthritis)

Septic arthritis is an acute onset bacterial inflammation, usually involving single joint (in > 90%), most often in knee joint and wrists. In IV drug abusers infection of spine and sacroiliac joints is more common.

ETIOLOGY

The most common organism of non-gonococcal arthritis is staphylococcus aureus. Other organisms include streptococci, gram negative bacilli such as E. coli and pseudomonas.

PREDISPOSING FACTORS

- **Hematogenous spread:** microorganisms reach the joint by hematogenous spread following bacteremia, so it is important to look for evidence of septic skin lesion, abrasions, endocarditis, IV drug abuse or throat or urinary tract infection.

- **Direct entry in the joint:** organisms can directly enter the joint following penetrating wounds, local osteomyelitis or joint injection.

CLINICAL FEATURES

- Sudden onset
- Typical presentation is single painful joint, often the knee. Other commonly affected joints are wrist, hip, shoulder and ankle. The joint is red, warm and swollen, with a demonstrable effusion and marked limitation of movement.
- Fever with chills in 80% of patients.

Diagnosis

- Blood culture: positive in 50% of cases.
- Aspiration of joint: Synovial fluid is purulent with neutrophil dominant, increased WBC (often more than 100,000/μL with > 90% neutrophils).
- Gram stain of synovial fluid is positive in 75% of cases. Culture / sensitivity of the fluid is also performed.
- Blood CP shows leukocytosis.

DIFFERENTIAL DIAGNOSIS

- Trauma
- Gout and pseudogout
- Reactive arthritis

TREATMENT

Joint immobilization, elevation.

Antibiotics

Antibiotics are given according to culture and sensitivity. Intravenous antibiotics for 2-3 weeks, followed by 9-10 weeks of oral antibiotics. It is usual to give two antibiotics to which the organism is sensitive.

Empirical treatment

Before the report of C/S is available.

- Intravenous ceftriaxone (Rocephin) 1-2 gm once daily plus cloxacillin (Orbenin) 1-2 g 6 hourly.
- Intravenous vancomycin 1g 12 hourly if methicillin resistant staphylococcus is suspected.
- Aminoglycoside should be given to IV drug abuser in which pseudomonas is suspected.

Drainage

- Daily drainage by needle until no further fluid is obtainable.
- Arthroscopic drainage and lavage is required if repeated needle aspiration fails to relieve the symptoms, failure to decrease the volume of effusion and there is no clearance of the bacteria from smear.

DIFFERENTIAL DIAGNOSIS OF ACUTE MONOARTHRITIS	
Infection • Bacterial • Viral • Fungal • Spirochetal	**Traumatic** • Hemarthosis • Fracture
Crystal arthropathy • Gout • Psudogout	**Degenerative** Osteoarthritis
Inflammatory • Rheumatoid arthritis • Juvenile idiopathic arthritis • Reactive arthritis • Psoriatic arthritis • Inflammatory bowel disease • Erythema nodosum • Palindromic arthritis • Paraneoplastic	**Bone disease** • Osteomyelitis • Osteonecrosis
Blood disorders • Leukemia • Hemophilia • Anticoagulants	**Tumors**

GONOCOCCAL ARTHRITIS

This is the one of the most common cause of septic arthritis in previously fit sexually active young adults (usually with history of contact with prostitutes). Recurrent infection should be evaluated for congenital deficiency of complements C7 and C8. Blood culture is positive in about 40% of cases. Culture is usually positive

also from genital organs, throat and rectum, although the joint fluid may be sterile. Synovial fluid gram- staining is positive in 25% of cases. Treatment is ceftriaxone 1g IV daily for 24-48 hours then ciprofloxacin 500mg 12- hourly for 7-10 days.

TUBERCULOUS ARTHRITIS

Tuberculous arthritis is invariably secondary to pulmonary or renal tuberculosis due to hematogenous spread of organism.

Pathology

- The synovial membrane and periarticular tissues become inflamed and edematous.
- Later there is destruction of cartilage which may lead to fibrous ankylosis.
- When spine is involved the infection may track along the fascial planes to produce psoas abscess.

Clinical features

- Usually single joint involvement affecting the hip or knee (30%) or other joints (20%) and spine (50%).
- Onset is insidious of pain and dysfunction of the joint. With swelling and synovial proliferation and restriction of movement.
- Malaise, anorexia, night sweats & weight loss.
- Spinal involvement may lead to compression of vertebre and paraplegia.

Investigations

- Synovial fluids: Synovial fluid culture & D/R
- Synovial biopsy
- X-ray: initially normal, later narrowing of the joint space.

Treatment

Antituberculous chemotherapy

MENINGOCOCCAL ARTHRITIS

This usually occurs as a part of generalized meningococcal septicemia. It is a migratory polyarthritis (one joint recovers & other involves). Organism cannot be isolated from synovial fluid. Treatment is with penicillin or ceftriaxone.

VIRAL ARTHRITIS

Organisms:

- Rubella virus (most common).
- Mumps virus
- Hepatitis B virus

This is particularly a complication of the rubella infection in young adult female.
This presents as bilateral, symmetrical polyarthritis & resolves within a few weeks in most of the cases.

SERONEGATIVE SPONDYLOARTHROPATHY

It is a group of diseases in which an inflammatory arthritis characterized by persistently negative test for rheumatoid factor (RF) is variably associated with a number of other common articular, extra articular & genetic features. These disorders develop usually before age 40. Inflammation of spine, or large peripheral joints, uveitis and absence of autoantibodies and striking association with HLA B-27 are characteristics of this group.
(NB: Very important topic for MCQs)

This group includes:

- Ankylosing spondylitis.
- Reactive arthritis (Reiter's syndrome).
- Psoriatic arthritis associated with psoriasis
- Enteropathic arthritis associated with ulcerative colitis and Crohn's disease
- Bechet's (Beshets) syndrome
- Juvenile chronic arthritis.

Etiology

Exact cause unknown, it is suggested that they may arise as an abnormal response to infection in genetically determined persons carrying HLA-B-27 antigen.

Pathology

In this inflammatory joint disease the is synovial and extra-synovial inflammation involves capsule, periarticular periosteum, cartilage and subchondral bone. Large central joints are particularly involved such as sacroiliac, symphysis pubis and intervertebral joints. Resolution of inflammation leads to extensive fibrosis and <u>joint fusion.</u>

CLINICAL FEATURES COMMON TO SERONEGATIVE SPONDYLOARTHROPATHY

- Asymmetrical inflammatory oligoarthritis (lower>upper limb).
- Sacroiliitis and spondylitis
- Familial
- No association with RA factor positivity
- Absence of nodules and other extra- articular features of RA.
- *Typical extra- articular features such as:* Conjunctivitis, buccal ulceration, urethritis, prostatitis, bowel ulcers, pustular skin lesions, anterior uveitis, aortic root fibrosis (causing aortic regurgitation, heart blocks) and erythema nodosum.

ANKYLOSING SPODYLITIS

This is a chronic inflammatory arthritis especially affecting sacroiliac joints and spine and characterized by progressive stiffening and fusion of the axial skeleton.

INCIDENCE

- Age: 20-30 years.
- Sex: Male & female ratio 4:1
- (More than 90% of affected persons carry the histocompatibility antigen HLA-B-27.

CLINICAL FEATURES

Symptoms

- *Onset:* Insidious, occasionally acute resembling lumbar disc protrusion.
- *Back pain:* Recurring episodes of low back pain and stiffness sometimes radiating to the buttocks or thighs. Pan is worse in early morning and after inactivity.
- *Chest Pain:* Chest pain aggravated by breathing results from involvement of the costoveertebral joints.
- *Heel Pain:* due to planter fasciitis.

Signs

- Failure to obliterate the lumbar lordosis on forward flexion.
- Pain on sacroiliac compression
- Tenderness over bony prominence such as iliac crest, ischial tuberosity and greater trochanter.
- Restriction of movements of lumbar spines in all directions.
- As the disease progresses, stiffness increases throughout the spine.
- Iritis occurs in 25% of patients.
- Aortic regurgitation, heart blocks, anterior uveitis.
- Pulmonary fibrosis of the upper lobes with progression to cavitation mimicking tuberculosis.

INVESTIGATIONS

- ESR – often raised
- RA factor absent.
- HLA B-27 in 90% cases. (present in 8% of normal population).

X-ray lumbar sine

- The sacroiliac joints are eroded with irregular margins and sclerosis of adjacent bone. As the disease advances, the sacroiliac joints may fuse.
- Syndesmophyte: It is a characteristic abnormality in the spinal column, characterized by calcification and ossification of the interspinous ligaments, appearing as continuous lines. Therefore called "tramline appearance".
- Vertebrae appear square as a result of erosion of their corners.

MANAGEMENT

Non-steroidal anti-inflammatory drugs NSAIDs.
These drugs are very effective in relieving night pain and morning stiffness.

- Indomethacin (Cap. Indocid) 25-50mg 3-times a day (most effective).
- Piroxicam (Feldene) 20mg at night.
- Phenylbutazone 300mg daily.

Regular exercise to prevent deformities.

- Sulhasalazine for long-term suppression in involvement of peripheral arthritis (not for sacroiliatis).
- Steroids: local steroid injection can be helpful for planter fasciitis.

REACTIVE ARTHRITIS
(REITER'S SYNDROME)

This syndrome consists of a triad of:

- Seronegative arthritis
- Non-specific urethritis
- Conjunctivitis (or uveitis)

It is sterile synovitis which develops within days or weeks of bacterial dysentery (due to salmonella, shigella, camylobacter) or exposure to sexually transmitted infection (chlamydia or ureaplasma urealyticum).

Male to female ratio is 20:1 and mostly young adults.
Associated with Hla B- 27 in 80% of cases.

CLINICAL FEATURES
The onset is typically acute with simultaneous development of urethritis, conjunctivitis (in 50%) and arthritis involving the large or small joints of the lower limbs 1-3 weeks following venereal infection or enteric fever or dysentery.

Arthritis:
The arthritis is typically in acute, asymmetrical, lower limb arthritis. Knee and ankle are the commonest site. There may be localized pain and tenderness in spine due to sacroilitis (in 20%). Arthritis is occasionally associated with non-articular inflammatory lesions e.g. planter fascilitis and Achilles tendonitis. Arthritis may persis for months or years.

Urethritis
This is associated with sterile discharge & mild dysuria. Circinate balanitis – a superficial penile lesion characterized by a circle of erythema with a ale center (rare).

Conjunctivitis
It is usually mild & bilateral occurring only one third of patients.

Keratoderma blennorrhagica:
Characterized by intense scaling of the 'skin of soles of the feet, resembling pustular psoriasis is seen in 10% of patients, with post-venereal Reiter's syndrome.

Systemic features
Fever and weight loss are common.
Carditis or aortic regurgitation may occur.

Investigations

- No specific investigation
- RA factor & autoantibodies are negative
- X-ray is of no value in acute stage but signs of permanent or progressive joint disease may be seen in sacroiliac as well as peripheral joints. Synovial fluid in inflammatory but sterile.

Treatment

- *NSAIDs* e.g. Indomethacin.
- Aspirate acutely inflamed joints and inject corticosteroids.
- *Tetracycline* for 3 months in cases of Reiter's disease associated with urethritis (due to chlamydia trachomatis).
- *Sulphasalizine* if no response to NSAIDs and tetracycline.

PSORIATIC ARTHRITIS

- This is a seronegative inflammatory arthritis found in pattern with psoriasis, a past or family history of psoriasis or with characteristic changes in the nails (nail pitting).
- Sometimes there is a single patch of psoriasis typically hidden in the scalp, gluteal cleft or umbilicus. (This may be your <u>short case</u> in exams and this is expected that after examination of joint you will look nails for pitting and search for psoriatic patch)>
- Arthritis develops in about 7% of patients with psoriasis. The onset is usually between the age of 25-40 years.

Clinical features
Arthritis involves distal interphalangeal joints usually associated with nail changes.

Extra articular features.

- Skin lesions: scaling lesions typically over extensr surfaces.
- Nail changes: pitting, onycholysis and horizontal ridging.
- Eye: iritis.

Investigations

- RA factor and ANA are negative.
- ESR is moderately raised.
- X-ray shows asymmetrical disease involving distal interphalangeal joints. There is relatively little periarticular osteopenia (that is common in RA).

Management

- NSAIDs
- Sulphasalazine or gold may be used in persistently symptomatic progressive arthritis without exacerbation of psoriasis. Methotrexate may be used when sulphasalazine has failed.
- Chloroquine should not be given because it may exacerbate skin disease and cause exfoliative dermatitis.
- Splints and prolonged rest are avoided because of the increased tendency to fibrous and bony ankylosis.
- Intra-articular injections may be used in persistently active and symptomatic joints.
- PUVA therapy may improve skin and joint disease.

ENTEROPATHIC ARTHRITIS

Arthritis associated with inflammatory bowel disease 12% in ulcerative colitis and 20% in Crohn's disease usually involves large joints of lower limb. Arthritis usually concides with exacerbations of underlying disease. Sometimes it may be associated with mouth ulcers, iritis, and erythma nodosum.

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

This is a multisystem connective tissue disease characterized by the presence of numerous autoantibodies, circulating immune complexes and widespread immunologically determined tissue damage.

PREVALANCE

- Peak age: between 20-40 years (reproductive life)
- Predominant sex: female to male ratio 9:1

ETIOLOGY

Exact cause of SLE is unknown. Following are the predisposing factors.

- Genetic predisposition
- Environmental factors e.g.
- Ultraviolet rays (sunlight).
- Drugs e.g. hydralazine, procainamide cause SLE more commonly, isoniazid, methyldopa, and chlorpromazine less commonly while phenytoin, carbamazipine, penicillamine, sulphasalazine, lithium and lovastatin probably.
- Viral infection – in animal models of SLE but not proved in humans.
- Pregnancy and puerperium (due to estrogen changes).

PATHOGENESIS

This is multifactorial disorder in which there is profound disturbance of immune regulation. A defect of suppressor T lymphocytes is associated with polyclonal B lymhocytes activation and the uncontrolled production of autoantibodies and immune complexes. Inflammatory process in SLE may occur by the two mechanisms.

- Autoantibodies react with cell nuclei therefore antigen-antibody reaction results in inflammation
- Deposition of immune complexes in the tissue causing vasculitis.

CLINICAL FEATURES

Most patients experience exacerbations interspersed with periods of relative remissions.

True remission with no symptoms and requiring no therapy occur in up to 20% of cases. Severity varies from mild and intermittent to persistent and fulminant.

Systemic manifestations

Fatigue, fever, anorexia and weight loss is prominent.

Musculoskeletal manifestations (in >90%).

- Joint involvement is the most common clinical feature. Almost all patients feel arthralgia and myalgia; most of them develop intermittent arthritis.
- Pain is often out of proportion to physical findings. Joints are painful but characteristically appear normal on clinical examination.
- Small joints are involved in symmetrical fashion just like in RA.
- Joint deformities are unusual and erosions are rare.
- Myopathy can be inflammatory (during periods of active disease) or secondary to glucocorticoid therapy.
- Ischemic necrosis of hip or knee is a rare complication.

Skin lesions (in 80%)

- *Erythema* on the cheeks of the face and across the bridge of the nose (butterfly rash) is characteristic of SLE. It is present in about 50 % of cases and is photosensitive.
- *Photosensitivity* – Prolonged exposure to sunlight can cause exacerbations of the disease.
- *Loss of scalp hair* occurs and is usually patchy.
- *Discoid Luus Erythematosus (DLE)* occurs in about 20% of cases of SLE and presents as circular erythematous lesions with scaliness and telangiectasia; scarring causes disfiguring. DLE occurs over scalp, ears, face, and sun exposed areas of arms, back and chest.
- *Vasculitic skin lesions* are purpura, subcutaneous nodules, nail fold infarcts, ulcer, urticaria, and gangrene of digits. Slightly painful ulcers in the mouth (occurring on hard & soft palate) and in nose are frequent.
- *Raynaud's phenomenon* may be severe enough to result in digital gangrene.

Kidneys (in 50%)

- Clinically significant renal involvement occurs in about 50% of cases but end stage renal failure occurs in minority of patients.
- Renal involvement ranges from insignificant proteinuria to nephrotic syndrome and renal failure. Urine analysis shows hematuria and proteinuria > 0.5 g day.
- Renal biopsy may provide information that affects therapy (type of glomerulonephritis, responding to steroids or not).
- Patients with rapidly deteriorating renal function require prompt and aggressive therapy with high dose corticosteroid and cytotoxic drugs. Biopsy is not necessary unless disease fails to respond.
- Patients with slow deterioration in renal function may show a high proportion of sclerotic glomeruli on biopsy; they are unlikely to respond to immunosuppressive therapies and are candidate for dialysis or transplantation.
- Hypertension – may occur due to either nephrotic syndrome or renal failure.

CNS (in 60%)

- Mild cognitive dysfunction is the most common CNS manifestation. Headache, depression and psychosis are also common.
- Focal infarcts, seizures, cerebellar dysfunction, aseptic meningitis, transverse myelitis, optic sensorimotor neuropathy may occur.
- Abnormal EEG occurs in 70% of cases.
- CSF shows elevated protein levels in 50% of patients. Oligoclonal bands may be found.
- CT scans and angiograms are most likely to be positive when focal neurological deficits are present.
- MRI is the most sensitive radiographic technique to detect changes of SLE; although changes are non -specific.

Vascular changes

Thrombosis to vessels of any size can be a major problem in SLE.

Hematological changes

- Anemia of chronic disease is present in most of the patients and some have Coomb's positive hemolytic anemia.
- Lymhopenia and mild thrombocytopenia is common.
- Lupus anticoagulant is an antibody against phospholipid causing antiphospholipid antibody syndrome (APLA) that results in thrombocytopenia, recurrent artrial or venous thrombosis, recurrent abortions and valvular heart disease. It is present in about 10% cases of SLE and requires anticoagulation.

Cardiovascular manifestations

- Pericarditis (most common) it rarely progresses to pericardial effusion and temponade.
- Myocarditis is often associated with pericarditis, manifests as tachycardia, cardiomegaly or heart failure. Severe valvular lesion, primarily of the mitral and aortic valves, may occur.
- A non-infective endocarditis involving mitral valve (called Libman-Sacks syndrome) occurs but rarely.
- Myocardial infarction may result from coronary arteritis, thrombosis, or premature atherosclerosis secondary to chronic corticosteroid use.

Respiratory changes

- Pleurisy and pleural effusion are common.
- Lupus pneumonitis causes fever, dysnea, cough. X-ray shows fleeting infiltrates.

Gastrointestinal manifestations

- Nausea, diarrhea and vague discomfort are common.
- Vasculitis of intestine is the most dangerous manifestation presenting with acute crampy abdominal pain, vomiting and diarrhea. Intestinal perforation can occur.

Eye changes

- Retinal vasculitis is serious manifestation; blindness can develop over a few days.
- Examination reveals areas of narrow retinal arterioles and white exudates adjacent to vessels.

REVIEW TABLE

CLINICAL FEATURES OF SLE

Musculoskeletal

- Arthralgia, non deforming arthritis.
- Involvement of small joints but less morning stiffness than in RA.
- Myopathy.

Skin

- Butterfly rash
- Alopecia
- Photosensitivity
- Discoid lupus
- Vasculitic lesions
- Raynaud's henomenon

Kidney

- Proteinuria, nehrotic syndrome
- Renal failure
- Hypertension

Vessels

Thrombosis

CNS

- Depression, psychosis
- Seizures, cerebral infarction (stroke)
- Blood
- Anemia, thrombocytopenia, lymphopenia
- Lupus anticoagulant.

Respiration

Pleurisy, pleural effusion, lupus neumonitis.

Eye

Retinal vasculitis – blindness

Blood

- Anemia, thrombocytoenia, lymhopenia
- ALA syndrome
- Slenomegaly
- Lymhadenopathy

LUPUS VARIANTS

Chronic Discoid Luus Erythematosus (DLE)
It is a benign variant of SLE in which skin involvement is often the only feature although systemic abnormalities may occur with time. The rash appears on face as well-defined erythematous plaque that progress to scaring and pigmentation.

Drug induced SLE
- It is usually characterized by arthralgia and mild systemic features, rashes and pericarditis, but often *without involvement of kidneys and CNS.*
- It usually disappears when the drug causing is stopped. Hydralazine and procainamide are the most common cause; other drugs involved are isoniazid, methyldopa, chlorpromazine, alpha interferon & penicillamine.
- All patients have ANA but Anti- dsDNA and hypocomplementemia are rare- a helpful feature to distinguish from idiopathic SLE.

SLE AND PREGNANCY
- SLE patients in remission are not likely to have exacerbations during pregnancy, however, women with active SLE, especially those with renal disease, have an increased frequency of exacerbations of their disease. Pre-eclampsia is a frequent complication of pregnancy.
- Fertility rates are normal in SLE but spontaneous abortion occur in 10-30% of women especially in those who have lupus anticoagulant and/or anticardiolipin antibodies.
- Disease flares in a small proportion, especially during the first 6 weeks postpartum.

DIFFERENTIAL DIAGNOSIS
- Rheumatoid arthritis
- Mixed connective tissue disease (MCTD)
- Drug induced SLE
- Various forms of dermatitis
- Neurological disorders such as epilepsy, multiple sclerosis and psychiatric disorders.

INVESTIGATIONS

Blood CP/ESR
Normocytic normochromic anemia
Leucopenia
Thrombocytopenia
Lymphopenia

ESR/C-eative protein
- ESR is raised and correlates with disease activity.
- C-reactive protein is normal.

Immunological findings

Antinuclear antibodies (ANA)
Serum ANA is positive in more than 95% of cases. It is the best screening test, however a positive ANA test is not specific for SLE; it may be positive in many other conditions. Therefore a positive ANA test supports the diagnosis of SLE but is not specific. A negative ANA test makes the diagnosis unlikely but not impossible.

ANTINUCLEAR ANTIBODIES: DISEASE ASSOCIATIONS
Following conditions are associated with positive ANA.

- Systemic lupus erythematosus (95%)
- Systemic sclerosis (80%)
- Sjogren's syndrome (605)
- Polymyositis and dermatomyositis (30%)
- Rheumatoid arthritis (30%)
- Still's disease (30%).

Occasionally seen in:
Autoimmune chronic hepatitis

PATTERNS OF ANA

Fluorescent pattern	*Disease association*
Rim, peripheral, shaggy	SLE
Homogenous	SLE and other autoimmune diseases
Speckled	Mixed connective tissue disease, SLE
Nucleolar	Scleroderma

Anti-double stranded DNA (anti-dsDNA)
are relatively specific for SLE but present in only 60% of cases; level fluctuates with disease activity. Antibodes to double stranded DNA may also be present in non-SLE patients such as other connective tissue diseases, chronic infections, chronic hepatitis and interstitial lung disease.

Anti-Sm (smith) antibodies
These antibodies are specific for SLE but present only in 30% of cases.

Frequency of autoantibodies SLE	
Antibody	*Frequency*
ANA	95-100%
Anti- double stranded DNA (anti-ssDNA)	60%
Anti-nDNA	50-60%
Anti- smith (anti-Sm)	30%
Anti-RNP (ribonuclear protein)	30%
Anti- SS-A	35%
Anti- SS-B	15%
antihistone	70% (95% in drug induced SLE)
RA factor	20%

.Antiphospholipid antibodies
There are three types of antiphospholipid antibodies that may be present in SLE:

1. Antıphospholipid antibodies causing false-positive test for syphilis.
2. *Lupus anticoagulant:* (in 7%) it is the risk factor for venous and arterial thrombosis and miscarriage. It is identified by prolongation of APTT.
3. *Anticardiolipin antibody*: (in 25%) causing recurrent venous or arterial thrombosis, recurrent fetal loss, or thrombocytopenia. Livedo reticularis, skin ulcers, mental status changes and mitral regurgitation may also present.

Drug induced SLE

- ANA is positive
- Antihistone antibodies in more than 95% of cases. Anti-
- Anti- dsDNA are usually negative.

RA factor
RA factor is positive in 20% of cases.

LE cells
LE cells are present in about 70% of patients with SLE, they are caused by antibody to deoxyribonucleoprotein (DNP).

VDRL
Serological tests for syphilis (VDRL) is falsely positive in about 30% of patients.

Serum complement
Serum complements level is low in active disease

Urinalysis
With active nephritis, urinalysis shows proteinuria, hematuria and red cell casts or granular casts. 24-hour urinary protein is also performed.

Serum creatinine
It should be performed periodically to assess the renal status.

MONITORING OF DISEASE ACTIVITY
High serum levels of ANA and anti- dsDNA, raised ESR and low levels of complements usually reflect disease activity, especially in patients who develop nephritis.

DIAGNOSTIC CRITERIA OF SLE

A patient is classified as having SLE if any 4 or more out of 11criteria are met.

1. **Malar rash**
   Fixed erythema, flat or raised, over the malar eminences.
2. **Discoid rash**
   Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur
3. **Photosensitivity**
   Skin rash due to unusual reaction to light.
4. **Oral ulcers**
   Oral and nasopharyngeal ulceration, may be painless.
5. **Arthritis**
   Non-erosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling, or effusion.
6. **Serositis**
   Pleuritis or pericarditis
7. **Renal disorder**
   Proteinuria greater than 0.5 g/d or cellular casts such as red cell, granular or tubular casts.
8. **Neurological disorder**
   Seizures or psychosis in the absence of offending drug or metabolic derangement.
9. **Hematologic disorder**
   - Hemolytic anemia or
   - Leucopenia (less than 4000/(mm) or
   - Lymphopenia (less than 1500/mm or
   - Thrombocytopenia (less than 100,000/mm in the absence of offending drugs.
10. **Immunologic disorder**
    - Anti - DNA antibodies in abnormal titer or
    - Anti-Sm antibodies or
    - Positive antiphospholipid antibodies.
    - Positive LE cells.
    - False positive VDRL for syphilis
11. **Antinuclear antibodies**
    An abnormal titer of ANA by immunofluorescence or an equivalent assay at any point in time in the absence of drugs known to induce ANAs.

PROGNOSIS

In most of the patients disease pursues a relapsing and remitting course. 10 year survival rates are > 85%. In some patients there is severe impairment of vital structures such as lungs, heart, brain or kidneys. Infections especially with opportunistic organisms have become the number one cause of death followed by active SLE, chiefly due to renal or CNS disease.

POOR RISK FACTORS

These risk factors cause 50% mortality in 10 years.

- High serum creatinine (> 1.4 mg/dl).
- Hypertension
- Nephrotic syndrome (>2.6g/d urinary proteins).
- Anemia hypoalbuminemia, and hypocomplementemia at the time of diagnosis.
- Low socioeconomic status.
- Thromboecytopenia, serious CNS involvement and presence of antibodies against phospholipids.

TREATMENT

There is no cure of SLE therefore management plan is;

- To control acute severe flares.
- To develop maintenance strategies in which symptoms are suppressed to an acceptable level, usually at the cost of some drug side-effects.

NSAIDs (Non-steroidal anti-inflammatory drugs)

Mild disease with arthralgia, arthritis, fever, and mild serositis may improve on NSAIDs.
Diclofenac (Voltra) 25mg TDS

Glucocorticoids

Systemic glucocorticods are reserved for patents with life-threatening, severily disabling manifestations of SLE such as CNS or renal involvement, myocarditis, pericarditis or significant thrombocytopenia.

In active disease, start prednisolone (Deltacortil) 1-2 mg kg day orally in 2-3 divided doses. After the disease is controlled, therapy should be consolidated to one morning dose; thereafter the daily dose should be tapered as rapidly as clinical disease permits. With remission of disease careful

attempts are made to withdraw steroids or to maintain patients on very low doses (10-15mg/day) or alternate day regimen.

Acutely ill patients, including those with proliferative glomerulonehritis can be started with 3-5 days of 1g IV "pulses" of methylprednisolone (Solu-Medrol) followed by maintenance daily or alternate day prednisolone.

Prednisolone (Deltacortil 5mg)
Active SLE with fever and pleurisy should be treated with prednisolone 1-2 mg daily. The dose should be reduced over the course of a few weeks to maintenance level of around 10-15 mg daily.

Methylprednisolone (solu- Medrol) 1g IV for 3 days required in patients with rapidly deteriorating renal function.

Chloroquine:
This is useful in the management of troublesome skin lesions or arthralgia that cannot be controlled with NSAIDs. Dose: hydroxychloroquine 400 mg daily.

Immunosupressive drugs:
Immunosupressive drugs such as azathioprine, cyclophosphomide, and chlorambucil are reserved for the following patients:

- Patients with severe focal or diffuse proliferative glomerulonephritis not responding adequately to corticosteroids.
- Patients in whom maintenance dose of steroid is so high as to cause severe side effects.
- Patients in whom disease is steroid resistant.

The combination of plasma exchange and cytotoxic drug therapy may be useful in some patients with severe steroid – resistant exacerbations.

MANAGEMENT PLAN OF SLE	
Arthralgia, arthritis, fever, and mild serositis	NSAIDs
Photosensitivity	Avoidance of sunlight, use of sunscreen
Rash	• Hydrochloroquine 400mg daily. • Sunscreen • Topical or intra-lesional glucocorticoids • Retinoids, dapsone
Arthritis	NSAIDs Hydroxychloroqione
Significant thrombocytopenia or hemolytic anemia	Steroids
Renal or CNS disease, pericaruitis or other organs involvement	Steroids
Rapidly deteriorating renal function	Pulse therapy with methylprednisolone in combination of pulse therapy with cyclophosphomide.
Renal disease	Plasma pharesis
SLE with antiphospholipid antibody syndrome who had previous thrombosis	Life – long warfarin

ANTIPHOSPHOLIPID ANTIBODY SYNDROME

The antiphospholipid antibody syndrome is associated with antibodies such as lupus anticoagulant and anticardiolipin antibodies. These antibodies have activity against enzymic reactions in the coagulation cascade that are dependent on platelet membrane (phospholipid in vitro) prolonging the APTT, however it is associated with increased tendency for thromboembolism and miscarriage (although there is prolonged APTT). A small portion of these patients have SLE. About 20% of strokes occurring under the age of 45 years are thought to be due to antiphospholipid syndrome and 27% of women who have had more than two abortions have the antiphospholipid antibodies.

FEATURES OF ANTIPHOSPHOLIPID SYNDROME

CNS • Cerebral ischemia, stroke • Epilepsy • Migraine • Transverse myelopathy • Chorea	**Obstetrics** • Recurrent spontaneous abortions • Intrauterine growth retardation
Cardiac • Myocardial infarction • Valvular disease • Pulmonary hypertension	**Skin** • Livedo reticularis
Renal • Renal vein thrombosis • Glomerular thrombosis	**GIT** • Bowel ischemia • Budd-Chiari syndrome
Blood • Thrombocytopenia • Hemolytic anemia	**Endocrine** 1. Adrenal thrombosis causing Addison's disease

Investigations

Anticardiolipin antibodies and lupus anticoagulant are detected by ELISA. ESR is normal and ANA is usually negative.

Management

Anticoagulants. Aspirin in mild cases and warfarin in severe cases. Aspirin and heparin are started from early phase of pregnancy (warfarin is contraindicated in pregnancy).

POLYMYOSITIS AND DERMATOMYOSITIS

Polymyositis

It is a disorder of muscle in which the pathological features are necrosis of muscle fibres together with evidence of regeneration and inflammation. It presents with proximal muscular weakness and wasting.

Dermatomyositis

When polymyositis is accompanied by skin rash, it is called dermatomyositis.

ETIOLOGY

The etiology is unknown. Patients with HLA-B8/DR3 appear to be genetically predisposed. Immunological & viral factors may be involved.

TYPES

Polymyostis and dermatomyositis can be divided clinically in five groups as following:

1. Adult polymyositis
2. Adult dermatomyositis
3. Adult polymyositis/dermatomyositis with malignancies
4. Childhood dermatomyositis
5. Polymyositis in other connective tissue diseases.

ADULT POLYMYOSITIS

Onset: usually insidious
Female to male ratio 3:1
Peak age: third to fifth decades.

Clinical features

1. *Muscle wasting & weakness* affecting the proximal muscles of the shoulder and pelvic girdles, manifested by difficulty in climbing stairs or rising from a chair. Sometimes onset

is rapid with rapid progression of muscular weakness. Involvement of pharyngeal, laryngeal and respiratory muscles can lead to dysphagia, dysphonia and respiratory failure within a few days.

2. *Muscle pain and tenderness* in about 50% of cases.
3. *Arthritis and arthralgia:* in about 50% of cases and may be presenting feature before muscular symptoms. The small joints of the hands are particularly affected. Joints are often swollen but the arthritis s intermittent and not progressive.
4. Raynaud's phenomenon is common.

ADULT DERMATOMYOSITIS

This is also more common in women. Acute or subacute muscle weakness is accompanied by periorbital edema and a characteristic violet *"helitrope rash"* on the upper eyelids.

In addition there may be photosensitivity, erythematous scaling rash in face, shoulders, upper arms, and chest with red patches over knuckles, elbows, and knees. Muscles pain, tenderness and weight loss are common along with arthralgia and mild arthritis.

INFLAMMATORY MYOSITIS ASSOCIATED WITH MALIGNANCIES

This type of myositis or dermatomyositis is seen after the age 40 years and is particularly associated with ovarian, gastric and nasopharyngeal carcinoma.

CHILDHOOD DERMATOMYOSITIS

This most commonly affects children between the ages of 4-10 years. Muscle weakness is usually associated with typical rash of dermatomyositis. Ulcerative skin vasculitis and recurrent abdominal pain due to vasculitis are also common features. Muscle atrophy, subcutaneous calcification and contractures may be widespread and severe.

ASSOCIATED WITH OTHER CONNECTIVE TISSUE DISEASES

SLE, RA, and systemic sclerosis may be associated with deforming arthritis, malar rash and skin sclerosis.

CAUSES OF SYMMETRICAL PROXIMAL MUSCLE WEAKNESS (PROXIMAL MYOPATHY)

Inflammatory causes

- Polymyositis
- Dermatomyositis
- Inclusion body myositis

Endocrine causes

- Hyperthyroidism
- Hypothyroidism
- Cushing's syndrome
- Acromegaly
- Diabetic amyotrophic (but usually unilateral)
- Steroid therapy

Metabolic causes

- Osteomalacia
- Paraneoplastic syndrome
- Carcinoma
- Periodic paralysis

Drugs/toxins

- Alcohol
- Fibrates (cholesterol lowering drug)
- Statins (cholesterol lowering drug)
- Penicillamine

Infections

- HIV, CMV
- Tuberculosis
- Schistosomiasis
- Toxoplasmosis

Genetic causes

Muscular dystrophy

INVESTIGATION

The diagnosis of polymyositis is made on the basis of three tests, two of which at least should be positive.

1. *Muscle enzymes:* Serum creatinine phosphokinase (CPK) & aldolase are raised.

2. *Electromyography (EMG): shows triad of changes of myositis:*
   - *Spontaneous fibrillation potential at rest*
   - *Polyphasic or short duration potential on voluntary contraction*
   - *Salvos of repetitive potentials on mechanical stimulation of the nerve.*

3. *Muscle biopsy:* shows necrosis & fibrosis of muscle fibres with swelling and disruption of muscle cells.

Other tests:

- ESR – raised in 5% of cases
- Normocytic normochromic anemia
- RA factor (in 50%) and antinuclear antibodies (commonly) positive.
- Antibodies to Jo-1 (rare)

MANAGEMENT

Bed rest combined with some exercise program such as physiotherapy to restore muscle power.

Corticosteroids:
Most patients respond to corticosteroids. Prednisolone, starting with 0.5-1mg/kg daily for at least one month and then reducing slowly to a maintenance dose of about 15 mg daily (adjust according to the serum level of muscle enzymes). Long term steroids are required. Withdrawal of steroids may lead to relapse.

Immunosuppressives: patients resistant to steroids are given immunosuppressivese.g. methotrexate or azathioprine.

Intravenous immunoglobulins: may be effective in dermatomyositis.

SYSTEMIC SCLEROSIS (SCLERODERMA)

This is a generalized disorder of connective tissue characterized by fibrosis and degenerative changes in the skin, blood vessels and visceral organs. Skin becomes tight and thick.

ETIOLOGY AND INCIDENCE

Etiology is unknown, may be immunological mediated.

- Female to male ratio 4:1.
- Peak age of onset: 30-50 years.

TYPES OF SCLERODERMA

Scleroderma is classified according to the degree and extent of skin thickening.

Systemic scleroderma

- Diffuse cutaneous scleroderma
- Limited cutaneous scleroderma (previously called CREST syndrome)

Localized scleroderma

- Morhea
- Linear scleroderma

In combination of other connective tissue disease.

- Overlap syndrome
- Mixed connective tissue disease (MCTD).

SYSTEMIC SCLERODERMA

Diffuse cutaneous scleroderma (40%)
It is characterized by the rapid development of symmetric skin thickening or tightening of proximal and distal extremity, face, and truck. These patients are at greater risk for developing kidney and other visceral involvement early in the course of disease.

Limited cutaneous scleroderma (60%)
It is characterized by symmetric skin thickening limited to distal extremities and face. Formerly it was called CREST syndrome the abbreviation of Calcinosis, Raynaud's phenomenon, Esophageal dysmotility, Sclerodactyly and Telangiectasia. The prognosis in limited scleroderma is better than diffuse variety because of much lower frequency of internal organ involvement, however after long time patient may develop pulmonary arterial hypertension or biliary cirrhosis.

DIFFERENCE BETWEEN DIFFUSE AND LIMITED SCLERODERMA		
FEATURES	***DIFFUSE***	***LIMITED***
Skin involvement	Distal and proximal extremities, face and trunk	Distal to elbows, face
Raynaud's phenomenon	Onset within one year or at time of skin changes	May preceed skin disease by years
Organ involvement	Pulmonary interstitial fibrosis, renovascular hypertensive crisis, GIT, heart	After 10-15 years of disease in less than 10% of patients. Also biliary cirrhosis
Nail fold capillaries	Dilatation and dropout	Dilatation without dropout
Antinuclear antibodies	Antitopoisomerase 1	Anticentomere

LOCALIZED SCLERODERMA

Localized scleroderma is limited to skin, subcutaneous tissue, and muscle. There is no systemic involvement. It affects primarily children. There are two types of localized scleroderma as following:

Morhea

It occurs as a single or multiple plaques of skin indurations and skin discoloration which evolve in sclerotic lesions.

Linear scleroderma

Sclerotic lesions appear as linear streaks or bands most commonly on extremities and less frequently on forehead, truck or frontoparietal scalp.

Involvement of various organs in systemic sclerosis

- Skin 90%
- Vascular system 80%
- Raynaud's phenomenon 80%
- Oesophagus 45%
- Lungs 40%
- Heart 35%
- Kidneys 25%
- Joints 20%
- Muscle 10%

CLINICAL FEATURES

Raynaud's phenomenon

Severe Raynaud's phenomenon is usually the presenting complaint and may precede other features by months or years. It presents with three color changes, initially pallor, then blue due to peripheral cyanosis and then red due to reactive hyperemia. There is also tingling sensation.

Skin changes

- Initially there is often non-pitting edema and induration associated with sausage swelling and restriction of movement of the fingers.
- Later skin becomes shiny with atrophy and ulceration of the finger tips.
- The skin of the face, limbs & trunk is also affected.
- In advanced cases: the face may become taut and "difficulty in opening the mouth". Tightening of skin over bony prominences also develops.

Musculoskeletal

- Arthralgia
- Mild non-erosive inflammatory arthritis
- Muscle weakness and wasting result from both disuse atrophy and low-grade myositis.

Gastrointestinal

Reflux esohagitis associated with a sliding hiatus hernia (common) presenting with heartburn or dyshagia.

Small bowel can be involved, producing malabsorption from bacterial overgrowth due to dilatation and atony.

Lungs
Lower-lobe fibrosis leads to cyst formation and honeycombing in advanced cases.

Heart
- Diffuse myocardial fibrosis with arrhythmias
- Pericarditis, cardiomyopathy, heart block and aortic valve lesion may occur.

Kidneys
Renal failure & malignant hypertension.

INVESTIGATIONS

Autoantibodies
- Antinuclear factor (ANF) is positive in 50% of cases with nucleolar or speckled pattern.
- Anticentromere antibody (ACA) is most commonly seen in limited scleroderma.
- Antibodies to topoisomerase I (Scl 70) called anti-Scl 70 are specific for diffuse scleroderma.
- ACA and anti- Scl 70 are only detected in serum of less than 50% patients with scleroderma. Presence of anti- Scl 70 may be a marker of pulmonary involvement.

Radiography
- *X-ray chest:* To look for established lung disease and heart size.
- *X-ray hands*: to look deposits of calcium around fingers and erosions of distal phalanges.
- *Barium swallow:* for impaired esophageal motility and reflux esophagitis.
- *High resolution CT scan:* to look fibrotic (interstitial) lung disease.

Blood count: normocytic normochromic anemia.
Urea and electrolytes: for renal function.
Urinalysis for proteinuria

MANAGEMENT
- No treatment only symptomatic management.
- Monitoring for detection of complications is required with measurement of blood pressure, blood counts, urinalysis and renal and pulmonary function tests regularly.
- Regular exercise to maintain flexibility of extremities, avoid frequent use of detergent soap that can cause dryness of skin, bath oils should be used to prevent dryness of skin. Massaging of skin my be helpful.
- Corticosteroids may produce some symptomatic relief in early stages where inflammatory edema or associated pericarditis, myositis and/or arthritis are predominant features. Starting dose is 40-60mg/d.
- Penicillamine has been reported to reduce the skin thickening and prevent development of significant organ involvement. Starting dose is 250mg/day then increasing at 1-3 month intervals to 1.5 g/d one hour before meal.
- Nifedipine and prostacyclin infusion may be helpful in severe Raynaud's phenomenon.
- ACE inhibitors are drug of choice in patients with renal crises and accelerated hypertension.

MIXED CONNECTIVE TISSUE DISEASE (MCTD)

The condition is characterized by overlapping clinical features suggesting SLE, progressive systemic sclerosis (scleroderma) and polymyositis and rheumatoid arthritis in association with very high titers of the circulating autoantibodies to nuclear RNP antigen (anti nRNP antibodies). With time in many patients, the manifestations evolve to one predominant disease such as scleroderma or SLE.

MCTD should not be diagnosed in patients who do not have high titer of anti-nRNP. In these patients term overlap syndrome is better in which clinical manifestations of more than one connective tissue disease are present without high titer of anti-nRNP. Now the term overlap syndrome is preferred to MCTD when features suggestive of connective tissue disease do not fit into a definite diagnostic category.
Antibodies to double stranded DNA (anti-dsDNA), anti-smith and anti- histone are negative.

Clinical features
- Age: 3rd or 4th decade.
- Sex: Female to male ratio 4:1
- Raynaud's phenomenon, puffy hands, arthralgia and myalgia are common presenting features.

- Patient may present with high grade fever, polymyositis, arthritis.
- Sclerodermal changes are usually limited to distal extremities.
- Some patients present with butterfly rash and other features of SLE.
- Deformities of hands similar to RA may be present but usually without erosions.
- Esohageal dysmotility is present in 70% of cases causing dysphagia.
- Lung involvement such as pleurisy, diffuse interstitial pulmonary fibrosis and pulmonary hypertension is common.
- About 25% patients develop proliferative glomerulonephritis.
- ESR & muscles enzymes are moderately raised.

Investigations

- Anemia, positive direct Coomb's test (in 60%)
- Leukopenia, thrombocytopenia
- Hypergammaglobinemia.
- RA factor is positive in 50% of cases.

Treatment

Depends on predominant disease.

SJÖGREN'S SYNDROME

Sjogren's (Shogrenz) syndrome is an autoimmune disorder of unknown etiology, develops as a result of chronic dysfunction of exocrine glands and is characterized by dryness of mouth, eyes, and other areas covered by mucus membranes.

It is predominantly a disorder of females, more than 90% patients are women; average age is 50 years.

This syndrome may occur alone however frequently associated with rheumatoid arthritis.

Clinical features

- *Dry eyes* (keratoconjunctivitis sicca) results from inadequate tear production caused by lymphocyte and plasma cell infiltration of lacrimal glands.
- *Parotid gland enlargement* occurs in one third of patients.
- *Dryness of mouth* (xerostomia) leads to difficulty in speaking and swallowing and to severe dental caries. There may be loss of taste and smell.
- Dysphagia, pancreatitis, pleuritis, neuropsychiatric, dysfunction and vasculitis may be present. Renal tubular acidosis and chronic interstitial nephritis may also occur.

CRYSTAL DEOSITION DISEASES

Three types of crystals are deposited in joints, each is associated with a characteristic clinical syndrome

- *Monosodium urate crystals deposition:* is associated with acute gout, typically affecting the big toe.
- *Calcium pyrophosphate crystals deposition* cause pseudogout which most often affects the knee.
- *Hydroxyapatite crystals deposition* causes acute calcific periarthritis which mostly affects shoulder.

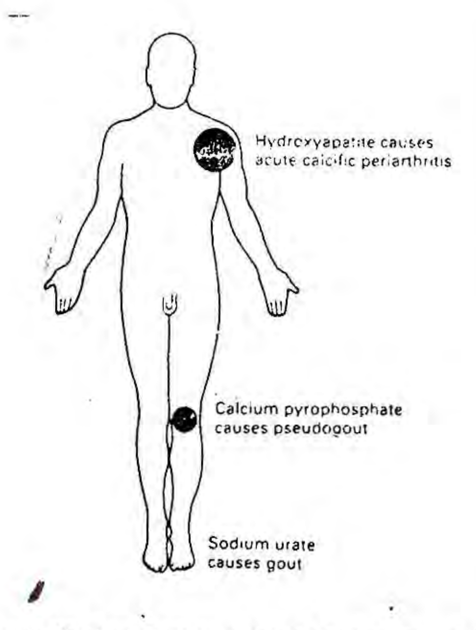


Fig. 8.18 The typical patterns of joint involvemen. seen in crystal deposition disease.

GOUT

Gout is an abnormality of uric acid metabolism that results in the deposition of sodium urate crystals in:

- *Joints* – causing acute gouty arthritis
- *Soft tissue* – causing tophi and tenosynovitis
- *Urinary tract* – causing urate stones.

The disease is 9-times more common in men as compared to women. Peak age 45 years.

PATHOGENESIS

The biochemical abnormality is hyperuricemia resulting from underexcretion (in 90%) or overproduction (in 10%) of uric acid.

FACTORS PREDISPOSING TO HYPERURICAEMIA AND GOUT

Diminished renal excretion of uric acid

- Renal failure
- Drugs
  - Diuretics, pyrazinamide
  - Low doses of aspirin
- Lead poisoning
- Hyperparathyroidism
- Myxedema
- Down's syndrome
- Lactic acidosis
  - Alcohol
  - Exercise
  - Starvation
  - Vomiting
  - Toxemia of pregnancy
  - Type I glycogen storage disease
- Unidentified inherited defect

Increased production of uric acid

- *Increased turnover of purines*
  - Chronic myeloproliferative disorders, e.g. polycythaemia vera,
  - Chronic llymhoroliferative disorders: e.g. chronic lymphatic leukaemia
  - Psoriasis – severe, exfoliative.
- *Increased purine synthesis de novo*
  - Hypoxanthine guanine hosphoribosyl transferase deficiency
  - Phosphoribosyl pyrophosphate synthetase overactivity
  - Glucose-6 phosphatase deficiency

CLINICAL FEATURES

Acute gouty arthritis

- Peak age of onset in men is 45 years.
- Usually after 20-30 years of sustained hyperuricemia.

Joints involvement:

Metatarsophalangeal joint of great toe (called podagra) is the site of first attack of acute gouty arthritis in > 70% of patients. Other joints are ankle, knee, small joints of hands & feet, wrist and elbow follow in decreasing order of frequency.

Inflammation:

Sudden in onset, severe pain & tenderness. The joint is hot, red, swollen with shiny overlying skin and dilated veins.

Frequency:

There is a tendency to have recurrent attacks with increase in frequency and duration progressively. Initial episodes are usually self-limited, however more than 50% of patients experience recurrent arthritis within 1 year of first attack. Later attacks tend to be more prolonged and severe and more commonly involve multiple joints.

Precipitating factors:

- Dietary excess
- Alcohol
- Starvation
- Diuretics
- Trauma, unusual physical exercise
- Systemic infection.

Chronic tohaceous gout

Recurrent attacks are followed by chronic gout in which there is progressive cartilage and bone erosions in association with deposition of tophi and secondary degenerative changes. Tohi are frequently found in the cartilage of ear, bursae and tendon sheaths. They appear 10-15 years after initial attack. Although tophi are painless, their presence in and around joints ultimately can limit joint mobility or cause severe joint deformities.

Urate stones

Uric acid stones develop in 10-20% of patients with gout. Gouty patients also have an increased

tendency of calcium oxalate stone formation. Patients with normal uric acid level may also have uric acid stones because of low solubility of uric acid.

Hyperurecemic acute renal failure

It usually results from _tumor lysis syndrome_ in patients with leukemia, lymphoma or after chemotherapy for these disorders. It manifests as oliguria, nausea, vomiting. Hyperuricemia, hyperkalemia, hyperphosphatemia and hypocalcemia.

INVESTIGATIONS

Synovial fluid examination

The affected joint is aspirated and the synovial fluid is examined under polarized – light microscopy. In acute gout, the presence of _negatively birefringent, needle-shaped urate_ crystals within the white blood cells.

Synovial fluid leukocyte count ranges from 1000-70,000/μL with a predominance of neutrophils.

Serum uric acid:

Serum uric acid is usually high (> 7.5mg/dl in more than 95% of patients) but it is important to know that in some patients it is not elevated, therefore normal uric acid level does not exclude gout. This is also important that the high uric acid level does not confirm the diagnosis of gout because asymptomatic hyperuricemia is very common.

Joint x-rays

Joint radiographs may show characteristic _punched-out erosions_ with an overhanging rim of cortical bone (rat-bite) associated with the soft tissue swelling due to urate tophi.

DIFFERENTIAL DIAGNOSIS

- Cellulitis
- Pseudogout
- Rheumatoid arthritis

MANAGEMENT

Rule of treatment is never treat acute arthritis and hyperuricemia simultaneously; first treat acute arthritis and hyperuricemia later. Sudden reduction of serum uric acid often precipitates further episodes of gouty arthritis.

ACUTE ATTACK

- **NSAIDs:** Indomethacin (Indocid) 25-50mg 3-5 times daily and after some relief reduce it to 25 mg 3-4 times daily. Usually 5-10 days treatment is required. Other NSAIDs are equally effective.
- **Colchicine** (Kolshicine): It is also effective for acute gout but less favored because 80% patients develop abdominal cramps, diarrhea, nausea and vomiting. Dose is 0.5-0.6mg/hour until pain is relieved or until diarrhea and abdominal pain develops.
- **Corticosteroids:** they are best in controlling acute attack but should be reserved for those patients who are unable to take oral NSAIDs. In monoarticular disease give intra-articular injection of triamcinolone 10-40 mg/d depending on size of joint. In polyarticular disease intravenous methylprednisolone 40mg/d tapered off over 7 days.

  Joint aspiration and Gram staining is necessary before corticosteroids because gouty and septic arthritis may coexist.
- **Analgesics**: opioids may be required for pain, aspirin should be avoided.
- **Bed rest** for 24 hours.

LONG-TERM THERAPY

Long-term therapy should be started when acute attack has settled. Long-term therapy is usually indicated when there are recurrent attacks of acute gout. These drugs are not effective for acute attack.

SIMPLE MEASURES TO REDUCE URIC ACID

- Weight reduction
- Reduction in alcohol intake
- Avoidance of foods containing high levels of purine e.g. meat, organ meat, seafood, beans, spinach, alcohol.
- Good fluid intake
- Withdrawal of drugs such as thiazides and salicylates.

DRUG THERAPY

Colchicine

When there are frequent attacks of gouty arthritis, chronic medical therapy with daily colchicine is recommended to prevent future attacks. Colchicine

is also used when uricosuric drugs or allopurinol are started to suppress the acute attacks that can be precipitated by abrupt changes in the serum uric acid level.

Reduction of serum uric acid

Two classes of agents can be used to reduce serum uric acid – uricosuric drugs and allopurinol. The choice of one or other depends on the result of a 24-hour urine uric acid determination. A value under 800mg/d indicates under-secretion of uric acid, which can be managed with uricosuric drugs. Patients who secrete more than 800mg/d are overproducers of uric acid and require allopurinol.

Uricosuric drugs

These drugs block tubular reabsortion of filtered uric acid, preventing the formation of new tohi and reduce the size of those already present. When given along with colchicine they reduce frequency of recurrence of acute gout. Uricoasuric drugs are not effective in renal insufficiency.

Indication: uricosuric drugs are indicated when there is increased frequency or severity of acute gout.

- Probenecid 0.5mg daily initially with gradual increase to 1-2g daily.
- Sulfinpyrazone 50-100 mg twice daily initially, gradually increasing to 200-400 mg twice daily.

Precaution: It is important to maintain daily urine output of 2000ml or more while giving uricosuric drugs to prevent precipitation of uric acid in urinary tract.

Allopurnol

Allopurinol (Zyloric) is a xanthine oxidase inhibitor that inhibits formation of uric acid. It is of special value in uric acid overproducers, in tophaceous gout, in patients not responding to uricosuric drugs and in gouty patients with uric acid renal stones. It is not recommended in asymptomatic hyperuricemia. Initial dose is 100mg/d for 1 week; increasing gradually to 200-300mg daily. Most important side effect is precipitation of acute gout. It should not be started for 4 weeks after the last acute attack because it may precipitate acute gout. Therefore cholchichine should be given prophylactically to prevent acute attack.

TREATMENT OF GOUT

Acute gout

- NSAIDs
- Corticosteroids

Chronic gout or recurrent attacks

- Uricosuric drugs: in undersecretors of uric acid (< 800mg in 24-hour urine collection).
- Allopurinol: in overproducers of uric acid (> 800mg in 24-hour urine collection).

Relationship of hyperuricemia with other diseases

Patients with hyperuricemia and gout have an increased incidence of:

- Hypertension
- Renal diseases (nehrosclerosis, tophi, pyelonephritis).
- Diabetes mellitus
- Hyertriglyceridemia
- Atherosclerosis

Although these relationships are not well understood.

PYROHOSHATE ARTHROPATHY

This is a type of crystal deposition disease characterized by deposition of calcium pyrophosphate dihydrate in joints. The acute attacks occur in about 25% of patients with the disease, known as **PSEUDOGOUT**.

Etiology

Exact cause unknown but there is an association with primary hyperparathyroidism, hemochromatosis, hypothyroidism and true gout.
Age – in old age at about 60 years.

Clinical features

Acute attack (pseudogout) is due to acute synovitis, commonly affects the knee joint with sudden pain & swelling. Other joints may be involved such as wrist, shoulder, ankle and elbow. The affected joint is warm and swollen

with a large effusion. Overlying erythema is common with very tender joint. Fever is also common. The attack resolves within weeks or months but recurs at regular intervals.

- *Chronic arthritis:* manifesting as chronic pain, morning stiffness and functional impairment. Knee joint is most commonly involved.

Investigations

- Serum calcium is normal
- Normal serum uric acid.
- ESR may be raised during an attack.
- Aspiration of synovial fluid and identification of crystals by polarized-light microscopy is diagnostic. Calcium pyrohoshate crystals are rhomboid – shaped and smaller than urate crystals (that are needle – shaped). The aspirated fluid is often turbid and may be blood stained
- X-ray shows chondrocalcinosis (calcification of cartilage) as linear calcification lying between and parallel with articular surfaces. Features of osteoarthritis may also present.

Management

- Rest
- NSAIDs
- Aspiration of fluid from an affected joint and an injection of corticosteroid (triamcinolone 10-40mg) .
- Colchicines for prophylaxis (it is less effective in acute attack in pseudogout.

BONE DISEASE

ACUTE PYOGENIC OSTEOMYELITIS

Osteomyelitis is a serious bone infection that should be properly diagnosed and treated in time.

ORGANISMS:

- Staphylococcus 90%.
- Streptococci, H. Influenza, and salmonella.

SOURCES

Hematogenous spread:

- Osteomyelitis results from bactremia and is associated with sickle cell disease, IV drug abuse, and in elderly.
- In sickle cell disease most common organism is salmonella.
- In drug abusers most common organism is S. aureus (pseudomonas and serrata may also be involved) and most common site is spine.
- Thoracic and lumber vertebrae are more commonly involved in elderly people with hematogenous spread. Risk factors are diabetes, IV canulla, and urinary catheters.
- Patient presents with fever, chills, pain and tenderness of bone.

Local infection

Prosthetic joint replacement, decubitus ulcer, and trauma may cause soft tissue infections that spread to bone. S. aureus and S. epidermidis are most common organisms involved.

Local signs of inflammation are present but fever and other signs of toxicity are absent.

Skin breakdown in the setting of vascular insufficiency

Patients with diabetes and vascular insufficiency are susceptible to developing osteomyelitis. The foot and ankle are most common sites. Infection originates from an ulcer or other break in skin. Bone pain and fever are often absent.

CLINICAL FEATURES

Acute & chronic: in acute form the onset is sudden with fever and severe pain at the site of bone infection. Chronic infection may be manifested by abscess within the bone (Brodie's abscess).

INVESTIGATIONS

- **X-ray**
  May be falsely negative in early phase.
  Initial radiographic findings may be soft tissue swelling and periarticular demineralization of bone, then there is erosion of bone.

- **CT, MRI and bone scan** are more sensitive than x-rays.
- **Blood culture:** positive in case of hematogenous spread.
- **Bone biopsy** and culture may be required.
- Culture from overlying ulcers, wounds, fistulas are unreliable.

MANAGEMENT

- Debridement of necrotic bone.
- Prolonged administration of antibiotics (4-6 weeks) A combination of quinolone (ciprofloxacin 750mg twice daily) plus rifampicin (300mg twice daily) is given in osteomyelitis caused by S. aurus .
- Vertebral body osteomyelitis and epidural abscess require urgent neurosurgical decompression.

Tuberculous osteomyelitis:

- It is due to hemoatogenous spread from a primary focus in the lungs or GIT. The spine is commonly involved (Pott's disease) with damage to the bodies of two neighboring vertebrae leading to vertebral collapse, and later paraventebral abscess formation (cold abscess).
- Pus can track along the tissue planes and discharge at thigh, chest or neck.
- Symptoms consist of local pain & later swelling due to collection of pus, along with the symptoms of tuberculosis.
- Treatment is antituberculous drugs & immobilization.

OSTEOPOROSIS

Osteoporosis is defined as reduced bone mas, microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and an increased risk of fracture. Bone is normally mineralized but is deficient in quantity, quality and structural integrity.

COMMON RISK FACTORS FOR OSTEOPOROSIS	
Endogenous	*Exogenous*
Female Asian Small stature Thin physique Family history Nulliparity Early menopause Advanced age	Low calcium intake Reduced physical activity Cigarette smoking Alcohol abuse Aluminum antacids Surgical menopause Steroid therapy

PATHOGENESIS

Osteoporosis is characterized by decrease in the amount of bone present to a level below which it is capable of marinating the structural integrity of the skeleton. The rate of bone formation is often normal, whereas the rate of bone resorption is increased. There is greater loss of trabecular bone than compact bone leading to crush fractures of vertebrae, fractures of neck of femur, and fractures of distal end of radius. Whatever the bone is present is normally mineralized.

RISK FACTORS OF OSTEOPOROSIS

Genetic

- Race
- Low body weight
- Family history

Endocrine

- Hypogonadism
- Early menopause
- Thyrotoxicosis
- Hyperparathyroidism
- Cushing's syndrome

Gastrointestinal disease
- Inflammatory bowel disease
- Malabsorption
- Chronic liver disease

Inflammatory disease
- Ankylosing sondylitis
- Rheumatoid arthritis

Drugs
- Corticosteroids
- Anticonvulsants
- Sedatives
- Heparin
- Excessive vitamin A or D intake

Substance abuse
- Alcohol
- Smoking

Lifestyle
- Poor diet/ low calcium intake
- Immobility

Inherited
- Osteogenesis imperfecta
- Homocystinuria
- Gaucher's disease
- Marfan's syndrome
- Ehlers- Danlos syndrome

Other
- Anorexia nervosa
- Protein calorie malnutrition
- Vitamin C deficiency
- Copper deficiency
- Multiple myeloma
- Neoplasia
- Pregnancy-associated
- Uncontrolled diabetes
- Rheumatoid arthritis

TYPES

- Type I is typical postmenopausal process
- Type II is more gradual senile osteoporosis that occurs in both sexes.

These types of osteoporosis should be differentiated from other causes of osteoporosis as given in previous column under the risk factors of osteoporosis.

CLINICAL FEATURES

- Osteoporosis is usually asymptomatic until fractures occur.
- In vertebral crush fractures a typical history would be the onset of severe pain in the dorsal spine which resolves slowly over a period of six weeks. Subsequent symptoms include loss of height from collapsed vertebrae, increasing kyphosis and abdominal protuberance.
- Other sites of osteoporotic fractures are the lumber vertebrae, distal radius and neck of the femur.

INVESTIGATIONS

Serum alkaline phosphatase:
Serum alkaline phosphatase is usually normal but may be slightly elevated especially after fracture.

Serum calcium, phosphate and parathyroid hormone are normal.

X-rays:
X- rays show decrease in bone density & fracture (may be). The principal areas of demineralization are the spine, and pelvis, especially in the femoral neck and head. Compression of vertebrae is common.

Bone density
Patients with suspected osteoporosis should undergo bone densitometry at spine and hip. CT densitometry or dual energy x-ray absorptiometry (DEXA) can determine bone density and are quite accurate. Bone densitometry score value of –2.5 or less, the diagnosis of osteoporosis is confirmed.

MANAGEMENT

General measures

- Adequate calcium intake (1500mg daily)
- Vitamin D intake
- Physical exercise.
- Avoid cigarette & alcohol.

Specific measures

Sex hormones

- Women with hypogonadism should be considered for hormone replacement therapy (HRT) with estrogen.
- Men with hypogonadism are treated with testosterone.

Selective estrogen receptor modulators (SERMs)

Raloxifene 60mg daily orally can be used by postmenopausal women in place of estrogen for prevention of osteoporosis.

- *Advantages over estrogen:* it does not cause endometrial hyperplasia, uterine bleeding, or cancer. It decreases risk of breast cancer.
- *Disadvantages*: bone density increases but 50% less than by estrogen, does not relieve vaginal dryness, does not improve hot flushes.

Bisphosphonates

These agents inhibit osteoclast – induced bone resorption.

Alendronate

Alendronate. (Fosamax) 10 mg daily or 70mg once weekly has been shown to increase bone mass and reduce the incidence of fracture. Reflux esophagitis and esophageal ulcers are main complication, therefore should be taken in the morning at least 30 min before breakfast with at least 8 oz of plain water and remain upright to reduce the risk of esophagitis. Calcium and vitamin D should also be given with bisphosphonates.

Pamidronate

Pamidronate is given in doses of 60mg by slow IV infusion in normal saline every 3 months in patients who cannot tolerate oral bisphosphonate.

Zoledronate

Zoledronate is given every 3-4 months in doses of 2-4 mg IV over 15 min, however it is very expensive.

Calcitonin

Nasal spray of calcitonin increases bone density .

RICKETS AND OSTEOMALACIA

These are metabolic bone diseases characterized by increased amounts of unmineralized osteoid and a decrease in the rate of bone formation.

Rickets

It is the form of osteomalacia that develops in children before eiphyseal closure & is characterized by defective maturation as well as mineralization of growing skeleton (epiphyseal cartilage).

Osteomalacia

It is characterized by defective bone mineralization, bone pain, muscle weakness and pathological fractures in adults.

PATHOGENESIS

- Rickets and osteomalacia develop due to vitamin D deficiency as a result of reduced dietary intake, vitamin D malabsorption or reduced sunlight exposure. The low levels of circulating 25(OH) vitamin D cause reduced production of the biologically active metabolite 1,25(OH) vitamin D by the kidney and this causes a reduction in calcium absorption from the intestine.
- The low calcium absorption stimulates parathyroid hormone secretion, which restores serum calcium levels towards normal by increasing bone resorption and renal tubular calcium reabsorption. The high level of parathyroid hormone also promotes phosphaturia, that causes phosphate deficiency.
- It is the combintion of calcium loss from the bone and phosphate depletion that causes impaired mineralization of bone.

CAUSES OF OSTEOMALACIA

VITAMIN DISORDERS

Vitamin D deficiency
- Decreased availability of vitamin D
- Insufficient sun light
- Malabsorption

Impaired conversion of 25(OH)D3 to 1,25(OH)D2
- Chronic renal failure
- Vitamin D dependent rickets type I (an autosomal recessive disorder in which there is defect in renal synthesis of vitamin 1,25(OH)D2.

Vitamin 1,25(OH)D2 receptor defect
Vitamin D dependent rickets type II (it is also autosomal recessive)

DIETARY CALCIUM DEFICIENCY

PHOSPHATE DEFICIENCY
- Decreased intestinal absorption
- Nutritional deficiency
- Malabsorption
- Increased renal loss in proximal renal tubular acidosis, Fanconi's syndrome, oncogenic osteomalacia

DISORDERS OF BONE MATRIX
- Fibrogenesis imperfecta
- Hypophosphatasia

INHIBITORS OF MINERALIZATION
- Aluminium antacids
- Bisphosphonate

RICKETS

Clinical features

Bone pain, reduction in growth and bowing of the long bones are characteristic of rickets with bossing of the frontal and parietal bones of skull and swelling of the costrochondral junctions (ricketry rosary).

Diagnosis

X-ray - shows widening of the growth plate with a cupped and ragged metaphysis.

OSTEOMALACIA

It is characterized by bone pain, tenderness, skeletal deformity and proximal myopathy which often results in a waddling gait and difficulty in climbing upstairs or getting out of the chair. Bone and muscular tenderness on pressure is common and focal bone pain may occur in association with fractures of the ribs and pelvis.

DIAGNOSIS

- *X-ray shows* typical pseudo-fractures (Looser's zones) in the ribs, long bones & pelvis. Looser's zones are linear areas of low density (less white) surrounded by sclerotic borders.
- *Biochemical changes:* lows plasma calcium, phosphate, Vit. D3 and low urine calcium. Alkaline phosphatase is raised.
- *Bone biopsy* is usually not required; however it is diagnostic of osteomalacia presenting as significant unmineralized osteoid.

MANAGEMENT

Vitamin D deficiency
- Vitamin D-alfacalcidol (Cap. One- Alpha Leo 0.25 and 1μg). Daily dosage 0.5-2.5 μg.
- Calcium carbonate 1-1.5g daily.

Phosphate deficiency
- Improve nutrition
- Oral phosphate supplement with vitamin D.
- Stop aluminum containing antacids.
- Human recombinant growth hormone reduces phosphaturia and may be added to above regimen.

PAGET'S DISEASE

Paget's disease of bone is characterized by one or more bony lesions having high bone turnover and disorganized osteoid formation. Involved bone becomes vascular, weak and deformed .

- It is the disease of elderly seldom seen before age 40, mostly identified incidentally on radiography or raised alkaline phosphatase; about 27% patients are symptomatic at the time of diagnosis.
- The pelvis, femur, tibia, lumbar spine, skull and scapula are principally affected.

Pathogenesis

- The primary abnormality is increased osteoclastic bone resorption which is accompanied by marrow fibrosis, increased vascularity of bone and decreased osteoblastic activity.
- Genetic factors are clearly important and family history is present in about 15% of cases.

Clinical features

- The classic presentation is *bone pain*, *deafness* and *pathologic fractures*.
- The bones become soft, leading to bowed tibias, kyphosis, and frequent fractures with slight trauma.
- If skull is involved, patient may report headache, *increased hat size* and *deafness* because affected bones enlarge and encroach the nerve foramina..
- Increased vascularity over involved bone causes increased warmth and can precipitate *high cardiac output failure.*
- Osteosarcoma is a rare complication.

Investigations

- Serum calcium and phosphate are normal but serum alkaline phosphatase is markedly high.
- Urinary hydroxyproline is also elevated in active disease.
- *X-rays:* the involved bone is expanded and denser than normal. Multiple fractures may be present in long bones.
- *Bone scan* can detect disease even before any x-ray changes are apparent.

Complications

- Fractures on minimal trauma.
- Kidney stones if there is immobilization.
- Spinal cord compression due to vertebral collapse.
- Osteosarcoma in long standing cases.
- High output cardiac failure due to increased vascularity.
- Cranial nerve palsies and stroke due to skull involvement.

Management

- Bisphosphonates or
- Calcitonin nasal spray.

NEOPLASTIC BONE DISEASE

The most common tumors are metastasis from the bronchus, breast & prostate. Symptoms are local bone pain over the area, fever & malaise.

Malignant neoplasms of bone

Metastasis (osteolytic):

- Bronchus
- Breast
- Prostate (often osteosclerotic as well)
- Thyroid
- Kidney
- Multiple myeloma

Primary bone tumors (rare; seen in the young)

- Osteosarcomas
- Fibrosarcomas
- Chondromas
- Ewing's tumor

INVESTIGATIONS

- **Bone scan:** picks up metastasis as hot areas before radiological changes occur.
- **X-ray** shows metastasis as osteolytic areas with bony destruction.
- **Serum alkaline phosphatase** is raised.
- Serum acid phosphatase raised in prostatic metastasis.
- Prostate specific antigen (PSA) is raised in prostatic carcinoma.

TREATMENT

Management of Metastasis

- Chemotherapy
- *Control of pain:* with analgesics, nerve blockade or local radiotherapy.
- *Orthopedic surgery* for pathological fractures.
- *Surgical decompression* for spinal metastasis.
- *Bisphosphonates:* they inhibit osteoclast activity and prevent bone resoption. Most tumors cause osteolytic lesions by local release of factors that increase osteoclastic activity causing bone resoption, therefore bisphosphonates are effective to prevent bone resorption.

BACK PAIN

HISTORY

The following factors should be considered.

Site

Lumbar pain. This is usually due to degenerative disease, disc prolapse; these are not commonly seen in the thoracic spine.

Thoracic pain: This is a characteristic site of osteoporotic crush fractures.

Radiation

Sciatic radiation of pain suggests root compression; however, sacroiliac pain can also radiate down the back of the thigh to knee.

Onset

- Sudden, e.g. disc prolapse or mechanical injury
- Gradual, e.g. ankylosing sondylitis.

Aggravating factors

Pain in the back and leg on walking and relieved by stopping is suggestive of intermittent claudication. It can be due to spinal stenosis.

Time pattern

- Disc disease is recurrent
- Ankylosing spondylitis is chronic.

Associated symptoms

There may be evidence of disease elsewhere.

EXAMINATION OF PATIENTS WITH BACK PAIN

Back

- Appearance – deformity
- Movement
- Palpation for tenderness

The nerve roots

- Straight leg raising; femoral stretch test
- Sensation, weakness.
- Reflexes, planter responses.

Complete physical examination

Look for abdominal masses, lymph nodes, iritis.

INVESTIGATIONS

- Plain X-rays
- Blood count and ESR
- Serum calcium phosphate, alkaline phsophatase.
- Serum acid hosphate.
- Protein electrohresis; immunoglobulins
- HLA-B27.
- Bone scan
- Radiculogram
- EMG
- CT scan/magnetic resonance imaging.

Features that suggest that back pain is serious

- Recent onset
- Weight loss
- Symptoms elsewhere, e.g. cough
- Localized pain in the dorsal spine
- Fever
- Raised ESR

NECK PAIN

- Ankylosing spondylitis
- Rheumatoid arthritis
- Cervical spondylitis
- Cervical disc prolapse
- Soft-tissue rheumatism
- Fibrositis

VASCULITIS

Vasculitis is an inflammation of the vessel wall. It is classified according to the size of vessel involved as following:

TYPES OF SYSTEMIC VASCULITIS	
Vessel size	*Vasculitis*
Large vessels	• Giant cell arteritis • Takayasu's arteritis
Medium vessels	• Polyarteritis nodosa • Kawasaki's arteritis
Small vessels	• Microscopic polyangitis • Wegener's granulomatosis • Churg- Strauss syndrome • Henoch- schonlein purpura • Essential cryoglobinemia

Other conditions associated with vasculitis

Infective
Infective endocarditis

Non-infective
- Vasculitis with rheumatoid arthritis
- Systemic lupus erythematosis
- Scleroderma
- Polymyositis/dermatomyositis
- Drug-induced Behcet's disease
- Goodpasture's syndrome
- Hypocomplementaemia
- Serum sickness
- Paraneoplastic
- Inflammatory bowel disease

LARGE VESSEL VASCULITIS

Polymyalgia rheumatica and giant cell arteritis are systemic illnesses of elderly. Both are associated with the finding of a giant cell arteritis on temporal artery biopsy.

Polymyalgia rheumatica

It causes sudden onset of severe pain and stiffness of the shoulder and neck, hips, lumber spine (limb girdle pattern). These symptoms are worse in the morning and persist from 30 minutes to several hours. There is no muscle weakness as in polymyositis.

- Because of stiffness and pain in shoulders, hip, and lower back, patients have trouble combing their hair, putting on a coat, or getting up out of a chair.
- Systemic features such as fever, malaise, weight loss are common.
- Patient is always above 50 years.

Differential diagnosis
- Polymyositis – proximal pain and weakness
- Polymyalgia rheumatica – proximal morning stiffness and pain.
- Myopathy – weakness, but no pain or stiffness.
- Rheumatoid arthritis
- Multiple myeloma
- Infective endocarditis.

Investigations
- *ESR*: markedly elevated and is hallmark of polymyalgia rheumatica.
- *Blood CP* : anemia is almost always present.
- *Temporal artery biopsy* It shows giant cell arteritis in 10-30% of cases but is not usually performed. Diagnosis is clinical.

Management
Prednisolone 10-20 mg/day. Dramatic response in 72 hours. Treatment duration is 6 months to 2 years.

Giant cell arteritis (temporal arteritis)

Giant cell arteritis is a systemic arteritis affecting medium sized and large vessels in patients over the age of 50 years. About 50 % patients with giant cell arteritis also have polymyalgia rheumatica.

Symptoms
- Severe headache, usually unilateral temporal or occipital.
- Tenderness of scalp (combing the hair may be painful).
- Claudication of the jaw when eating. Throat pain.

Signs
- Temporal artery is usually normal on examination but may be enlarged, tender, nodular or pulsatile.
- Occlusive arteritis of ophthalmic arteries causes sudden painless temporary or permanent *visual loss*.

- Asymmetry of pulse, murmur of AR if giant cell arteritis has affected aorta or its main branches.
- Other features : dry cough, mononeuritis multiplex, or fever of unknown etiology (WBC count is normal).
- Thoracic aortic aneurysm occur 17 times more frequently in patients with giant cell arteritis.

Investigations
- ESR and C-reactive protein: very high
- Interleukin- 6 is the most sensitive indicator of disease activity.
- Blood count: normocytic normochromic anemia.
- Serum alkaline phosphatase (liver source) is elevated in 20% of patients.
- *Temporal artery biopsy:* It is a definitive diagnostic test. It should be performed before or within 36 hours of starting corticosteroids. Lesion is patchy and the whole length of the biopsy must be examined; an adequate biopsy specimen is required (2 cm in length). Temporal artery biopsy is positive in 80-85% in unilateral while 90-100% in bilateral temoral artery biopsy.

Treatment

Corticosteroids produce dramatic reduction of symptoms within 24-48 hours of starting treatment. Starting dose is high that is tapered slowing in weekly steps.
Prednisolone 60mg daily

Takayasu's arteritis (pulseless disease)

It is a chronic inflammatory granulomatous vaculitis of elastic arteries such as aorta and its main branches.
It is more common in females (female to male ratio 8:1) under the age of 40 years.

Symptoms

Symptoms depend on stage of disease:
Early inflammatory symptoms
Fever, arthralgia, myalgia, pain over the involved artery.
Late occlusive symptoms
Syncope, dizziness, amaurosis fugax, stroke, angina, pulmonary hypertension and claudication. Hypertension due to proximal renal artery stenosis or aortic coarctation is present in 25% of patients..

Signs

Examination shows diminished peripheral pulses, asymmetrical blood pressure measurement on two limbs and hypertension .

Investigation

CP/ESR: anemia, mild leucocytosis, raised ESR.
Aortography is usually required to demonstrate stenosis in the aortic arch or its branches. The most commonly involved vessels are subclavian artery, descending thoracic aorta, renal artery, carotid artery and mesenteric arteries. MRA may be used in suspected case of Takayasu's arteritis for screening.

Treatment
- Most patients respond in early stage to high dose corticosteroid 1-2mg/kg/day with control of symptoms and limiting the progress of disease. Immunosupressive drugs such as methotrexate or cyclophosphomide may be required if steroids are ineffective.
- Bypass of the occluded or aneurismal segments is the usual surgical approach.

MEDIUM-SIZED VESSEL VASCULITIS

Polyarteritis nodosa (PAN)

It is a narcotizing vasculitis affecting medium-sized arteries. All age group are affected, with peak age fourth and fifth decade. Male to female ratio is 2:1.

Types
- Hepatitis –B related PAN: vasculitis is associated with circulating immune complexes containing hepatitis – B surface antigen.
- Hepatitis –B unrelated PAN.

Clinical features

Systemic features

Fever, malaise, weight loss and myalgia.

Features of organ infarctions

As following:

Neurological
Mononeuritis multiplex due to arteritis of vasa nervorum.

Abdominal

- Abdominal pain due to arterial involvement of abdominal viscera, mimicking acute cholecystitis, pancreatitis, appendicits.
- Gastrointestinal hemorrhage occurs due to mucosal ulceration.

Renal

- Hematuria and proteinuria
- Hypertension, acute/chronic renal failure.

Cardiac

- Coronary arteritis causes myocardial infarction, heart failure.
- Pericarditis may occur.

Skin
Palpable purpura, subcutaneous hemorrhage and gangrene.

Lung
Chest pain, consolidation or variable pulmonary infiltrates.

Investigations

- *CP/ESR:* anemia, leukocytosis and raised ESR.
- *Biopsy:* of affected organ shows fibrinoid necrosis of vessel walls with microaneurysm formation, thrombosis and infarction.
- *Angiography:* shows multiple aneurysms in hepatic, intestinal or renal vessels.

Treatment

- Antiviral therapy if hepatitis – B is present.
- Immunosupressive therapy with corticosteroids: usually the combination of corticosteroids with immunosuppressive drugs such as azathioprine or cyclophosphomide leads to improvement in majority of cases.

Kawasaki's disease

It is an acute systemic vasculitis involving medium sized vessels, affecting mainly children under five years of age. It is very frequent in Japan.

Clinical features

1. Fever persisting more than 5 days
2. Bilateral conjunctival congestion
3. Erythema of lips, buccalmucosa, and tongue.
4. Cervical lymphadenopathy
5. Polymorphous exanthema
6. Erythema of palms and soles
7. Coronary dilatation.

5 out of 6 features or 4 out of 6 plus coronary dilatation are required for diagnosis.

Investigations:
Leukocytosis, thrombocytosis, raised ESR, ANCA may be positive in some children, echocardiography or angiography to detect coronary arteries dilatation.

Treatment:
Aspirin 5mg/kg/d, high dose intravenous immunoglobulin. Steroids should be avoided because of risk of worsening of coronary artery dilatation. Athrosclerosis and ischemic heart disease are complications of dilated coronary arteries.

SMALL VESSEL VASCULITIS

Vasculitis of arterioles, capillaries and venules can be divided into two groups:

1. *ANCA (antineutrophilic cytoplasmic antibody) positive vasculitis*
    - Wegener's granulomatosis
    - Churg- Strauss granulomatosis
    - Microscopic polyangitis
2. *Non-ANCA – positive vasculitis*
    - Henoch-Schonlein purpura.

Wegener's granulomatosis

1. It presents with upper and lower respiratory tract lesions in association with a focal segmental, narcotizing glomerulonehritis.
2. Upper respiratory lesions may be recurrent rhinitis, epistaxis, sinusitis, or serous otitis media.
3. Lower respiratory tract lesions may be cough, hemoptysis, chest pain, dysnea, and cavitating lung disease.

Churg-Strauss syndrome

1. It manifests as allergic rhinitis and nasal polyposis for years, and then asthma develops.
2. Pulmonary infiltrates and eosinohilia are the major features of this syndrome.
3. About 70% patients develop cutaneous nodular or papular rash, and about 60% have accompanying mononeuritis multiplex.
4. Sural nerve biopsy often reveals vasculitis of vasa nervosum, together with perineural eosinohil infiltration.
5. Cardiac manifestations account for half of deaths, and include myocardial infarction, cardiomyoathy and pericarditis.

Microscopic polyangitis

It presents as narcotizing glomerulonephritis and/or lung hemorrhage.

Henoch-Schonlein purura

1. It is common in children and is associate with abdominal pain and an acute arthritis affecting one or more joint.
2. The disease frequently follows respiratory tract infection and lasts usually for less than 3 months. Boys are more affected than girls.
3. Purpura is found characteristically over the buttocks and lower legs..
4. Angioedema is also present in about 50% of patients. Intussuscetion, rectal bleeding and renal involvement are features of severe cases.
5. nephritis occurs in 40% of cases
6. corticosteroids are effective for gastrointestinal and joint involvement but nephritis requires IV steroids and immunosuppressives.

Treatment of ANCA positive small vessel vasculitis

1. Microscopic polyangitis, Wegener's granulomatosis are treated with high dose oral prednisolne 1mg/kg/day and cyclophosphamide 2mg/kg/day.
2. Churg-Strauss syndromes frequently responds to corticosteroid alone.
3. Treatment is continued usually for 1-2 years with low dose prednisolone and azathioprine.
4. Plasma exchange is undertaken in patients with severe or resistant cases.
5. Intravenous immunoglobulin is considered when other treatment fail.

BACHET'S SYNDROME

This is a vasculitis of unknown etiology that characteristically involves venules. It is more common in Mediterranean countries and Japan and strongly associated with HLA- B51.

Clinical features

- Recurrent oral ulcers are universal, genital ulcers are less common.
- Eye lesions: usually bilateral uveitis and retinal vasculitis.
- Skin lesions: erythema nodosum, acneform nodules.
- CNS: pyramidal signs, brain stem lesions or hemiparesis.
- Positive pathergy test: hyper- reactivity at the site of minor trauma.

Management

- *Oral ulcers*: topical steroids.
- *Erythma nodosum:* colchicines.
- *Resistant oral or genital ulcers:* thalidomide (however it is teratogenic and neurotoxic).
- *Systemic disease:* steroids and immunosuppressives.

BLOOD DISORDERS 8

COMMON INVESTIGATIONS IN BLOOD DISEASES

COMPLETE BLOOD COUNT (CBC)

Complete blood count (CBC) or complete picture (CP) is one of the most frequently requested test by clinicians. In Pakistan we mostly use term CP. Blood anticoagulated with EDTA is rapidly processed through an automatic analyzer and then peripheral film is performed for differential count and to examine cellular morphology.

NORMAL VALUES FOR BLOOD CELLS

Cell type	Mean	Range
Hemoglobin	Men 15.5 g/dl Women 14.0 g/dl	12-16g/dl 13.5-17.5g/dl
Hematocrit	Men 47% Women 41%	
Reticulocytes	1% 60,000/µl	0.5-1.5% 35,000-85,000/ µl
Mean corpuscular volumes (MCV)	89 fl	82-98 fl
Platelet count	250,000/ µl	150,000-400,000/ µl
Total white count	7400/ µl	4500-11,000/ µl
Neutrophils	**59%** 4400/ µl	1800-7700/ µl
Lymphocytes	**34%** 2500/ µl	1000-4800/ µl
Monocytes	**4%** 300/ µl	
Eosinophils	**3%** 200/ µl	
Basophils	**1%** 65/ µl	

Interpretation of blood CP

We get a lot of information from blood CP, details are given in relevant sections, here is the brief description.

- *Hemoglobin*: deficiency is called anemia, then look MCV to diagnose cause of anemia. Increased hemoglobin is called polycythemia; it may be due to some stimulating factors or malignancy of red cells (polycythemia rubra vera).
- *Reticulocyte count:* these are immature cells that increase after blood loss or in anemic patient after starting iron therapy, while in bone marrow failure there is no increase in reticulocyte count.
- *White cell count:* increased in infection, inflammation, and malignancy while decreased in severe infection or bone marrow failure. Increase or decrease in WBC is according to the particular component such as increase in neutrophils is called neutrophilia and decrease is called neutropenia. Following are the causes of neutrophilia, neutropenia, eosinophila, basophilia, monocytosis and lymphocytosis.

CAUSES OF NEUTROPHILIA	
Infection	Bacterial, fungal
Inflammation	Gout, RA, inflammatory bowel disease
Infarction	MI, pulmonary embolism
Malignancy	Polycythemia, CML, lymphoma
Physiological	Exercise, pregnancy

CAUSES OF NEUTROPENIA	
Infection	Viral, salmonella, malaria
Drugs	NSAIDs, antithyroid, captopril, anticonvulsant, antimalarial, sulphonamides
Autoimmune	Connective tissue diseases
Alcohol	

CAUSES OF EOSINOPHILIA	
Allergy	Asthma, eczema
Infection	Parasitic infection
Drug allergy	Sulphonamide
Connective tissue disease	Polyarteritis nodosa
Malignancy	Lymphoma

CAUSES OF BASOPHILIA	
Myeloproliferative disease	Polycythemia , CML
Inflammation	Allergy, inflammatory bowel disease
Iron deficiency	

CAUSES OF MONOCYTOSIS	
Infection	Bacterial , tuberculosis
Inflammation	Connective tissue diseases, inflammatory bowel disease
Malignancy	Solid tumors

CAUSES OF LYMPHOCYTOSIS	
Infection	Viral, pertussis
Lymphoproliferative disease	CLL, lymphoma
Post- splenectomy	

CAUSES OF LYMPHOPENIA	
Drugs	Steroids, cytotoxic drugs
Inflammation	Connective tissue diseases
Malignancy	Lymphoma
Renal failure Sarcoidosis	

Terms describing abnormal blood film appearance and their meanings (microscopic features of blood CP)	
Microcytosis	Size of RBC is small seen in iron deficiency anemia, sideroblastic anemia and thalassemia
Macrocytosis	Size of RBC is more than normal. Causes are megaloblastic anemia, liver disease and alcoholism.
Hypochromia	RBCs contain less amount of hemoglobin.
Anisocytosis	RBCs are of different size, mostly seen in megaloblastic anemia.
Poikilocytosis	RBCs are of different shapes, usually reflects dyserythropoiesis
Target cells	Present in liver disease, hyposplenism and thalassemia
Polychromasia	Indicates production of new cells by bone marrow.
Punctate basophilia (basophil stippling)	Abnormally damaged young RBCs, mostly present in chronic lead poisoning, and beta thalassemia.
Howell- Jolly bodies	Their presence indicate hyposplenism or aspenism, also increased in megaloblastic anemia
Nucleated red cells (normoblast)	Immature cells indicating rapid formation of RBCs as in leukemia, hemolysis, myelofibrosis
Hypersegmented polymorphs	Five or more lobes in more than 3% of polymorphs. Usually in megaloblastic anemia.
Leukoerythroblastic	Immature RBCs and WBCs are present due to bone marrow irritation as in severe hemolysis, bleeding. Also in myelofibrosis.

TESTS FOR BLEEDING DISORDER

Test	Normal range	Situations in which test is abnormal
Platelet count	150-350x 10^9/l	Thrombocytopenia
Bleeding time	< 8 minutes	Thrombocytopenia Aspirin Von Willebrand disease
Prothrombin time	12-14 seconds	Deficiency of factors II, V, VII, X Liver disease Warfarin therapy DIC
APTT	30-40 seconds	Deficiency of factors II, V, VIII, X, XI, XII. Hemophilia A and B Von Willebrand disease DIC
Fibrinogen concentration	1.5-3.0 g/dl	Congenital hypofibrinogenemia

TESTS FOR THROMBOTIC DISORDER

- Prothrombin
- Protein C
- Protein S
- Antithrombin III
- Factor V Leiden
- Thrombin time
- Anitiphospholipid antibodies such as lupus anticoagulant and anticardiolipin antibody.
- Serum homocysteine

BONE MARROW EXAMINATION

Bone marrow examination is performed in adults from the posterior iliac crest. Marrow may be simply aspirated or a bone marrow biopsy (trephine biopsy) is performed. Trephine is superior for assessing marrow cellularity and infiltration.

Main indications

Marrow disorders

- Leukaemias
- Lymphomas
- Secondary carcinoma
- Myeloproliferative disorders

Cytopenias

- Neutropenia
- Thrombocytopenia
- Anemia-complex cases or aplasia

SPLENOMEGALY

CAUSES OF SPLENOMEGALY

Congestion

- Cirrhosis
- Hepatic vein occlusion
- Portal or splenic vein thrombosis
- Congestive cardiac failure
- Constrictive pericarditis

Infections

Acute infections

- Typhoid, septicemia, endocarditis
- Infectious mononucleosis, hepatitis, CMV

Chronic infections

Tuberculosis, brucellosis

Parasitic infestation

Malaria, kalazar, schistosomiasis, trypanosomiasis

Fungal infection

Histoplasmosis

Inflammation

SLE, , sarcoidosis, Felty's syndrome

Hematological disorders

Hemolytic anemias

- Hemoglobinopathies such as thalassemia
- Autoimmune hemolytic anemia
- Megaloblastic anemia

Myeloproliferative disorders

- Chronic myeloid leukemia
- Myelofibrosis
- Polycythemia vera
- Essential thrombocythemia

Neoplastic

Leukemia, lymphoma, metastatic cancer

Storage disease

Gaucher's disease, Niemann – Pick disease

Miscellaneous

Hyperthyroidism, amyloidosis, cysts.

CAUSES OF SPLENOMEGALY ACCORDING TO THE SIZE

Massive splenomegaly
More than 8 cm below the costal margin or reaching to umbilicus.

- Malaria
- Kalazar
- Chronic myeloid leukemia
- Primary lymphoma of spleen
- Portal hypertension

Moderate
About 4-8 cm below the left costal margin or large but not reaching to umbilicus (usually 2-4 fingers).

- All causes of massive splenomegaly
- Portal hypertension (cirrhosis, CCF)
- Leukemia (acute or chronic)
- Lymphoma
- Thalassemia
- Gaucher's disease

Small
Just palpable or 2-4 cm below costal margin (1-2 fingers).

- Causes of massive and moderate splenomegaly
- *Hematological:* polycythemia, hemolytic anemia, megaloblastic anemia.
- *Infections*: malaria, infective endocarditis, hepatitis, infectous mononucleosis.
- *Connective tissue disease:* SLE, RA, polyarteritis nodosa.

Splenomegaly with anemia
- Hemolytic anemias such as thalassaemia
- Leukemia, lymphoma
- Cirrhosis of liver (portal hypertension)

Hepatosplenomegaly
- Chronic liver disease
- Myeloproliferative disorders
- Lymphoproliferative disorders such as chronic lymphocytic leukemia, lymphoma.
- Miliary tuberculosis
- Brucellosis, CMV infection
- Megaloblastic anemia
- Gaucher's disease
- Amyloidosis

EFFECTS OF SPLENOMEGALY

Local effects:
Abdominal discomfort, with back pain, and abdominal bloating due to stomach compression due to moderate to massive spleen. Pressure on bladder or colon may cause symptoms.

Hypersplenism
It is defined as increased removal of blood cells by the spleen. This syndrome is combination of:
- Detectable spleen
- One or more cytopenia (anemia, leukopenia, thrombocytopenia).
- Normal or hypercellular bone marrow.
- Normalization after splenectomy.

INDICATIONS OF SPLENECTOMY
- Autoimmune hemolytic anemia
- Felty's syndrome
- Gaucher's disease
- Hereditary spherocytosis
- Idiopathic thrombocytopenic purpura
- Thrombotic thrombocytopenic purpura.
- Myelfibrosis
- Thalassemia

CAUSES OF LYMPHADENOPATHY

Infective
- *Bacterial*
  Streptococci, staphylococci, brucellosis tuberculosis.
- *Viral*
  Infectious mononucleosis, HIV, hepatitis
- *Protozoal*
  Toxoplasmosis, leshminiasis, filariasis
- *Fungal*
  Histoplasmosis, coccidiodomycosis

Neoplastic
- Primary: Leukaemias, lymphomas
- Secondary: head and neck, Lung, breast, thyroid, stomach.

Connective tissue disorders
- Rheumatoid arthritis
- Systemic lupus erythematosus (SLE)
- MCTD
- Dermatomyositis

Other
- Sarcoidosis, Amyloidosis

Drugs
- Phenytoin, Allopurinol, Carbamazepine

ANEMIAS

Anemia may be defined as a state in which the blood hemoglobin level is below 13.5 g/dl in an adult male and below 11.5 g/dl in an adult female.

Symptoms

- Fatigue
- Headache
- Faintness
- Breathlessness
- Angina of effort
- Palpitation
- Intermittent claudication

Signs

Non-specific

- Paler skin, conjunctiva & mucous membrane
- Tachycardia
- High volume pulse
- Ankle edema
- Cardiac failure
- Systolic flow murmur

Specific

- Koilonychia (spoon shaped nails) – in iron deficiency.
- Jaundice – in hemolytic anemia
- Bone deformities – in thalassemia major
- Leg ulcers – in sickle cell anemia

CLASSIFICATION

There are two classifications

- According to the cause.
- According to the morphology of red cells.

Classification according to the cause:

- Inadequate production of RBC
- Blood loss anemia
  - Acute – due to acute hemorrhage
  - Chronic – due to GIT bleeding, menorrhagia.
- Excessive destruction of RBC (hemolysis)

CAUSES OF INADEQUATE PRODUCTION OF ERYTHROCYTES

Deficiency of essential factors
Iron, vitamin B12 or folate

Toxic factors

- Inflammatory disease
- Hepatic and renal failure
- Drugs

Endocrine deficiencies

- Hypothyroidism
- Hpoadrenalism
- Hypopituitarism
- Hypogonadism
- Reduced production of erythropoietin

Invasion of bone marrow
Leukaemia, secondary carcinoma, fibrosis

Disorders of developing red cells

- Sideroblastic anemia
- Neoplastic disorders of erythropoiesis
- Other idiopathic refractory anemias
- Herediatary disorders of hemoglobin synthesis (thalassaemia).

Failure of stem cells
Hypoplastic and aplastic anaemia

CLASSIFICATION ACCORDING TO THE MORPHOLOGY

This is the most useful classification and mostly anemias are classified according to this classification.

MICROCYTIC (MCV > 100fl)

- Iron deficiency anemia
- Thalassemia minor
- Sideroblastic anemia
- Lead poisoning

MACROCYTIC (MCV > 100 fl)

- **Megaloblastic:** due to vitamin B12 & folic acid deficiency. Severely macrocytic anemia (MCV > 125) is almost always due to megaloblastic anemia).
- **Macrocytic without megaloblastic**: due to alcohol excess, cirrhosis of liver, hypothyroidism and reticulocytosis, marrow infiltration and myelodysplastic syndrome.

NORMOCYTIC (80-100 fl)

- Aplastic anemia (bone marrow failure)
- Myelodysplastic syndrome
- Anemia of chronic disease such as connective tissue disease, tuberculosis, chronic renal failure.
- Endocrine disorders e.g. hypothyroidism, hypopituitarism & Addison's disease.
- Hemolytic anemias
- Malignancy
- Malnutrition

MICROCYTIC ANEMIA

Causes of microcytic anemia

- Iron deficiency anemia
- Thalassemia minor
- Sideroblastic anemia
- Lead poisoning
- Anemia of chronic disease

IRON DEFICIENCY ANEMIA

Iron deficiency anemia develops when there is an inadequate amount of iron for hemoglobin synthesis.

CAUSES OF IRON DEFICIENCY

- Poor intake
- Decreased absorption (Celiac disease, gastrectomy)
- Increased demand in growing adolescents and pregnancy.
- Blood loss from GIT due to:
  - Hookworm infestation
  - From erosions associated with anti - inflammatory drugs, peptic ulcer or neoplastic disease.
  - Hemorrhoids
- Blood loss from irregular or excessive menstruation.

CLINICAL FEATURES

1. Features of anemia described earlier
2. Features due to iron deficiency in the tissues producing epithelial changes are the following:
   - Brittle nails & nail cracking are common but flattening or concavity of nails (koilonychias) may be present.
   - Atrophy of the papillae of the tongue
   - Angular stomatitis
   - Brittle hair.
   - *Plummer-Vinson Syndrome:* consisting of iron deficiency anemia and dysphagia, due to esophageal webs usually in middle aged women.

DIAGNOSIS

Diagnosis is made with history, examination and investigations.

1. History: Ask the patient about:

- Dietary intake
- Regular-self medication with aspirin (which may give rise to GIT bleeding)
- Presence of blood in the feces (which may be due to hemorrhoids or carcinoma of the lower bowel).
- In woman ask about duration & flow of menstruation, the occurrence of clots & number of sanitary towels used.

Examination:

- Look anemia and features of iron deficiency.
- Palpate spleen to find out chronic liver disease as a cause of chronic blood loss.
- Rectal examination and proctoscopy.

INVESTIGATIONS

Blood CP: The red cells are

- Microcytic (MCV < 80 fl)
- Hypochromic (MCH < 27 pg)
- Poikilocytosis (variation in shape)
- Anisocytosis (variation in size)
- Target cells are also seen.

Serum ferritin

Iron deficiency is best confirmed by measuring serum ferritin. It reflects the amount of stored iron, which is *depleted first* even before change in red cell size or decrease in serum iron. Normal value is 30-300 µg/L in males and 15-200 µg/L in females. A ferritin value less than 30 µg/L nearly always indicates absent iron stores.

Serum iron & iron-binding capacity

Serum iron falls and the total iron-binding capacity (TIBC) rises as compared to normal. (Note: these parameters are not much helpful because serum iron may be low during infection and TIBC may be reduced due to poor nutrition).

Bone marrow

Erythroid hyperplasia with ragged normoblast are seen in marrow in iron deficiency anemia. Bone marrow stain indicates iron depletion.

Examination of stool & urine

Examine for hookworm infestation & schistosomiasis.

Diagnostic features of Iron deficiency
- Hemoglobin: variably reduced
- Mean cell volume: reduced
- Erythrocyte count: normal or reduced
- Blood film: hypochromia, micrycytosis, oval and elliptical cells, poikilocyte in more severe cases.
- Leukocyte count differential: normal
- Platelet count: normal or raised
- Bone marrow iron stores: empty
- Plasma transferrin: raised
- Plasma iron: reduced
- Serum ferritin: reduced

DIFFERENTIAL DIAGNOSIS

In all other causes of microcytic anemia, iron stores are normal or increased.

MANAGEMENT

- Treatment of the cause.
- Iron replacement.

Oral iron:

- Tab. Ferrous sulphate (Iberet) 500mg daily
- Cap. Ferrous gluconate (Sangobion) 250 mg daily

Administration after food minimizes gastric side effects.

Side effects:

Nausea, vomiting, epigastric pain, constipation or diarrhea.

Monitoring: Response to iron can be monitored using reticulocyte count (that increases in a week) and hemoglobin levels with an expected rise in hemoglobin of 1g per week. Usually hemoglobin returns to baseline within 2 months but continue iron therapy for 3-6 months.

Parenteral:

Indications:

- When patient is unable to take iron by mouth because of gastric pain, vomiting or diarrhea.
- For getting rapid response in conditions e.g. anemia late in pregnancy and before surgery
- Malabsorption
- GIT conditions which may be aggravated by oral iron e.g. peptic ulcer & ulcerative colitis.
- Parenteral therapy should be given in a proper hospital with expert staff. Always give test dose before injection and wait for 15 minutes for reaction. Anaphylactic reaction may occur and all facilities should be available for resuscitation. Parenteral therapy is very commonly used in anemic patients with pregnancy by obstetricians , therefore thorough knowledge is required for administration and adverse effects.

Intramuscularly

Inj. Jectofer (75mg), 1.5 mg/kg/day (in upper outer quadrant of buttock).

Single daily or alternate day injection is given to restore hemoglobin levels to normal and replenish iron stores based on the following table.

Hemoglobin g/dl	5	6	7	8	9	10	11
No. of injections	24	22	20	17	14	12	10

Precautions

- Oral iron should be discontinued 24 hours before injection.
- Change to new needle after filling the syringe.
- Introduce the needle deep intramuscularly.
- Check that needle point is not in a blood vessel by loosening the needle from syringe, if blood does not appear from the needle in 5-10 seconds, the syringe is reattached and injection completed.
- Do not massage over the injection site.

Side effects

- Pain and staining at the site of injection.
- Cardiac arrhythmias

Intravenous infusion:

Inj. Venofer (1 ml = 100mg iron and 5ml= 100mg iron) may be given by slow IV injection or IV infusion. Total required dose is calculated and Venofer is given accordingly in divided doses once a week. It is not suitable for intramuscular injection or as a single total dose infusion.

Test dose: Before administration of therapeutic dose of Venofer in a new patient, a test dose of 1-2.5 ml is given by IV slowly in 5-10 min and wait for at least 15 minutes for allergic reaction and hypotension; if patient becomes hypotensive then no further infusion should be given. For mild allergic reaction anti- histamine may be used.. Facilities for CPR should be available.

Infusion For IV infusion 1ml of Venofer is diluted in 20ml of normal saline (5ml in 100ml and 25ml in 500ml saline) in 4-6 hours. Maximum dose in one infusion is 25 ml.

Total iron deficit: body wt (kg) X 2.3 X (target Hb-actual Hb in g/L) X 0.24 + 500mg (for stores).

Target hemoglobin is 150 g/L.

SIDEROBLASTIC ANEMIA

It is an inherited or acquired disorder characterized by dyserythropoiesis, inability of iron utilization and therefore iron overload and ring sideroblasts in the bone marrow.. There is a disordered accumulation of iron in the mitochondria of erythroblasts because it can not be utilized due to defects in enzymes involved in hem synthesis, resulting in formation of ring of iron granules around the nucleus seen with Prussian blue stain of bone marrow.

Patients have no specific features other than those related to anemia.

CAUSES OF SIDEROBLASTIC ANEMIA

Inherited

X-linked disease – transmitted by females

Acquired

Primary (one type of myelodysplastic syndrome)

Secondary

- Drugs, e.g. isoniazid, phenacetin
- Alcohol abuse
- Lead toxicity
- Myeloproliferative disorders
- Myeloid leukaemias
- Other disorders: carcinoma, RA, megaloblastic and hemolytic anemias, malabsorption.

Diagnosis

- Blood film shows dimorphic picture (both normal & microcytic cells).
- Bone marrow shows erythroid hyperplasia, signs of ineffective erythropoiesis. Iron stain (Prussian stain) shows generalized increase in iron stores and the presence of ring sideroblasts.
- Serum iron and tranferrin saturation are high.

Management

- Blood transfusion in severe anemia.
- The withdrawal of drugs or alcohol if they are causative agents. In some cases folic acid or pyridoxine may improve iron utilization.

ANEMIA DUE TO LEAD POISONING

Blood features in anemia due to lead poisoning are:

- **Sideroblastic anemia** due to inhibition by lead of enzymes involved in haem synthesis including ALA synthetase.
- **Hemolysis** due to red cell membrane damage.
- **Basophillic stippling** (punctate basophillia): blood film shows red cells with small, round, blue particles due to aggregates of RNA in red cells due to inhibition by lead of pyrimidine 5-nucleotidase which normally disperses residual RNA to produce a diffuse blue staining seen in reticulocytes on blood film.

ANEMIA OF CHRONIC DISEASE

This type of microcytic anemia develops in patients with chronic infections such as infective endocarditis, tuberculosis, osteomyelitis, rheumatoid arthritis, SLE, polymyalgia rheumatica and malignancy.

Mechanism

- There is decreased release of iron from bone marrow to developing erythroblasts.
- Decreased response to erythropoietin.
- Decreased red cell survival.

Investigations

- Serum iron and TIBC are low.
- Serum ferritin is normal or high due to inflammatory process.
- Iron is present in marrow but not in developing erythroblasts.

Treatment

- Treatment of underlying cause
- No response to iron therapy

NORMOCYTIC ANEMIA

Causes
Normocytic normochromic anemia is seen in the following conditions

- *Chronic diseases*
- *Endocrine disorders* e.g. hypopituitarism, hypothyroidism and hypoadrenalism
- *Blood disorders:* e.g. aplastic anemia & some hemolytic anemias.
- *Acute blood loss*: following acute blood loss before iron stores are depleted.

Mechanism
Exact mechanism is not known but there may be reduction of erythropoietin & reduced red cell survival (as in chronic renal failure),
Decreased release of iron from the bone marrow to developing erythroblasts.

Investigations

1. *Blood C.P:*
   - RBC are normocytic & normochromic
   - Hemoglobin level is low.
2. Serum iron & iron binding capacity both are low (D/D iniron-deficiency anaemia iron is low but iron binding capacity becomes raised).
3. Serum ferritin (iron stores) normal. (D/D in iron deficiency it is low).

Management
Patients do not respond to iron therapy. Treatment is that of underlying disorder.

MACROCYTIC ANEMIA

Macrocytosis with megaloblastic changes
- Vitamin B12 deficiency
- Folic acid deficiency

Macrocytosis without megaloblastic changes
(Vit B12 & folic acid level normal)

<u>Physiological</u>
- Pregnancy
- New born

<u>Pathological</u>
- Alcohol excess
- Liver disease
- Reticulocytosis
- Hypothyroidism

MEGALOBLASTIC ANEMIA

Megaloblastic anemia is characterized by presence of erythroblasts in the bone marrow with delayed nuclear maturation because of defective DNA synthesis. These erythroblasts are large in size therefore called megaloblasts.

Etiology
- Vitamin B12 deficiency
- Folic acid deficiency

Pathogenesis
For the proliferation of hemopoietic tissue DNA is required in large amount. Both Vit. B12 and folic acid are necessary for DNA synthesis. Therefore deficiency of either B12 or folic acid leads to reduced DNA synthesis which results in delayed or stopped cell division in bone marrow. Cell division is sluggish, but cytoplasmic development progresses normally, therefore megaloblastic cells tend to be large, with an increased ratio of RNA to DNA. Megaloblastic erythroid cells tend to be destroyed in the marrow. Thus the marrow cellularity is often increased but production of RBCs is decreased (this abnormality is called ineffective erythropoiesis). Associated with changes in red cells, changes also occur in WBC precursors (giant metamyelocytes) and in megakaryocytes.

The massive destruction of marrow cells from dyserythropoiesis liberates large quantities of enzymes including LDH, which rises to very high levels in blood.

MEGALOBLASTIC ANEMIA DUE TO VITAMIN B12 DEFICIENCY

Vitamin B12 is found in meat, fish, egg and milk but not in plant. Its absorption from lower ileum is facilitated by gastric intrinsic factor, synthesized by gastric parietal cells. The intrinsic factor forms complex with Vit. B12. This complex is taken up at special binding sites in the ileum where the Vit. B12 is released into the ileum cells; intrinsic factor is not absorbed. After absorption Vit. B12 is bound to a carrier protein in the plasma & transported to tissues and taken up by cells as required. Vit. B12 is stored in the liver that is enough for 3 years.

CAUSES OF VITAMIN B12 DEFICIENCY

Low dietary intake
In true vegetarians.

Impaired absorption

Stomach

- Intrinsic factor deficiency due to pernicious anemia, gastrectomy
- Congenital deficiency of intrinsic factor without gastric atrophy (rare)

Small bowel

- Crohn's disease, ileal resection.
- Vitamin B12 may be removed from the gut by bacterial overgrowth in stagnant loops
- Parasites such as the fish tapeworm.

PERNICIOUS ANEMIA

It is the megaloblastic anemia due to vitamin B12 deficiency as a result of failure of secretion of intrinsic factory by stomach due to atrophy of gastric mucosa. It is an autoimmune disease and in about 50% of patients antibodies to intrinsic factor can be detected. There is an association with other autoimmune diseases particularly thyroid disease, Addison's disease and vitiligo.

It is the commonest cause of Vit. B12 deficiency.
Age incidence : 45-60 years.

CLINICAL FEATURES

FEATURES OF MEGALOBLASTIC ANEMIA DUE TO VITAMIN B12 DEFICIENCY

Symptoms

1. *Onset* – insidious
2. *Features of anemia* e.g. pallor, weakness, tachycardia and dyspnoea. Anemia may be severe.
3. *Yellow discoloration:* due to mild jaundice caused by excessive breakdown of hemoglobin due to ineffective erythropoiesis in the bone marrow.
4. *Mucosal changes:* Red sore tongue due to glossitis and angular stomatitis may be present. Diarrhea and anorexia due to changes in GI mucosa.
5. *Neurological features*
   - Polyneuropathy presenting with symmetrical paraesthesia in the fingers and toes.
   - The posterior columns of spinal cord next become impaired causing loss of vibration sense & proprioception (early) and patients complain of difficulty with balance.
   - In more advanced case cerebral function may be altered. Progressive weakness and ataxia. Paraplegia may occur.
   - Dementia and optic atrophy may also occur.

Signs

- Anemia
- Skin with lemon-yellow tint due to unconjugated hyperbilirubinemia due to increased RBC destruction
- Spleen may be palpable
- Purpura due to thrombocytopenia may be present.
- Low grade fever due to anemia itself or due to infection.
- Red sore tongue (glossitis) and angular stomatitis are sometimes present.
- CNS examination shows signs of a polyneuropathy or subacute combined degeneration of spinal cord.

Blood picture

- *Hemoglobin* – low.
- *MCV* – raised usually between 110-140 fl. However it is possible to have B12 deficiency with a normal MCV. When iron deficiency or thalassemia coexist with B12 deficiency MCV is usually normal.
- Peripheral film shows anisocytosis, poiklocytosis.
- WBC & platelet count may be low showing pancytopenia.
- *Neutrophils* are hypersegmented (6 lobes)
- *Reticulocyte* count is low.

Bone marrow

It shows marked erythroid hyperplasia, abnormally large cell size, giant metamyelocytes.

Serum vitamin B12

It is usually low below the normal level of 150 350 pg/ml. Most patients with B12 deficiency have serum B12 levels less than 100 pg/ml.

Serum LDH: elevated

Serum unconjugated (indirect) bilirubin is increased.

Vitamin B12 absorption test

Schilling test is the traditional test to document decreased oral absorption of vitamin B12 that is characteristic of pernicious anemia.

<u>SCHILLING TEST</u>

Give 1000 μg B12 (Inj Neurobion) IM to saturate B12 binding plasma transport proteins.

<u>Stage 1</u>

Radiolabelled B12 1μg is administered orally to fasting patient, and a 24-hour urine collection is performed to determine how much B12 is absorbed and subsequently excreted. Normally more than 7% of dose is present in urine; while patients with impaired absorption usually have less than 3% present in urine.

<u>Stage 2</u>

Give radiolabelled B12 together with intrinsic factor.

If pernicious anemia is the cause of vitamin B12 deficiency, the combined use of vitamin B12 and intrinsic factor should correct the abnormally low absorption.

If excretion is still abnormal, lesion is in the terminal ileum or there is bacterial overgrowth.

Vitamin B12 deficiency due to bacterial overgrowth can be corrected by antibiotic therapy.

DIAGNOSTIC FEATURES OF PERNICIOUS ANEMIA

Diagnostic findings

- Very low serum vitamin B12, often less than 100 pg/l
- Anti-intrinsic factor antibodies in serum (present in 50%)

Corroborative findings

- Macrocytic dysplastic blood picture
- Megaloblastic marrow
- Abnormal vitamin B12 absorption test corrected by addition of intrinsic factor (Schilling test).

DIAGNOSTIC FEATURES OF A MEGALOBLASTIC ANAEMIA

- *Haemoglobin:* Often reduced, may be very low
- *Mean cell volume*: Usually raised, commonly > 120 fl.
- *Erythrocyte count:* Low for degree of anemia
- *Blood film*: Oval macrocytosis, polkilocytosis, red cell fragmentation, neutrophil hypersegmentation.
- *Reticulocyte count:* Low for degree of anaemia
- *Leukocyte count*: Low, normal or reduced
- *Platelet count:* Low, normal or reduced.
- *Bone marrow*: Increased cellularity, megaloblastic changes in erythroid series, giant metamyelocytes, dysplastic megakaryocytes, increased iron in stores, pathological non-ring sideroblasts.
- *Serum iron:* Elevated
- *Iron binding capacity*: Increased saturation
- *Serum ferritin*: Elevated
- *Plasma LDH:* Elevated, often markedly

TREATMENT

General measures

- *Blood transfusion* – When hemoglobin is very low such as 4g/dl. Transfusion should be given in the form of packed cell volume (PCV) along with frusemide 40-80 mg. If whole blood is transfused, there may develop high output cardiac failure (volume overload).
- *Treatment of infection*
- *Packed platelets*: if the patient presets with purpura.

Vitamin B12

Patients with pernicious anemia are treated with parenteral therapy.

Inj. Vitamin B12 100µg daily for first week, weekly for first month and then monthly for life.

- Clinical improvement may occur within 48 hours. Reticulocytosis can be seen 2-3 days after therapy peaking 5-7 days and normalization of blood picture within 2 months.
- Improvement of the polyneuropathy occurs within 6-12 months but longstanding symptoms (more than 6 months) are usually irreversible.
- Hypokalaemia may occur which requires replacement therapy.

Iron

Tab. Ferrous sulphate 200 mg T.D.s: In some patients rapid regeneration of the blood depletes the iron reserves of the body, to prevent it ferrous sulphate should be given soon after the commencement of treatment with B12.

MEGALOBLASTIC ANEMIA DUE TO FOLIC ACID (FOLATE) DEFICIENCY

Folic acid is present in vegetable and animal foodstuffs. Its deficiency results in megaloblastic anemia. The most common cause of folic acid deficiency is inadequate dietary intake; malabsorption of folic acid is rare because it is absorbed from the entire GIT.

CAUSES OF FOLIC ACID DEFICIENCY	
Nutritional <u>Poor intake</u> • Old age • Starvation • Alcohol excess <u>Poor intake due to anorexia</u> • GI diseases such as Celiac disease, Crohn's disease • Cancer	**Excess utilization** <u>Physiological</u> • Pregnancy • Lactation • Prematurity <u>Pathological</u> • Hemolysis • Malignant disease with increased cell turnover • Inflammatory disease • Homocystinuria • Dialysis
Antifolate drugs • Phenytoin • Methotrexate • Pyrimethamine • Trimethoprim	**Malabsorption** Small bowel diseases

CLINICAL FEATURES

- Features of anemia and underlying cause
- Glossitis may occur
- Unlike with B12 deficiency there is no neuropathy.

DIAGNOSIS FEATURES OF FOLIC ACID DEFICIENCY

Diagnostic findings
- Low serum folate levels/fasting blood sample)
- Red cell folate levels low (but may be normal if folate deficiency is of very recent onset)

Corroborative findings
- Macrocytic dysplastic blood picture
- Megaloblastic marrow

MANAGEMENT

Folic acid

- Tab. Folic acid 5 mg orally per day.
- Maintenance dose 5 mg/week
- Prophylactically in pregnant women where there is rapid cell turnover and in patients taking methtrexate.
- Folic acid should never be given before vitamin B12 in B12 deficiency anemia because folic acid can aggravate or precipitate neurological features of B12 depletion.

APLASTIC ANEMIA

Aplastic anemia is defined as peripheral blood pancytopenia (low RBC, WBC, platelets) with aplasia (inability to produce blood cells) of the bone marrow.

Aplastic anemia is due to reduction in the number of pluripotential stem cells. Failure of one cell line may occur. A full blood count demonstrates pancytopenia. Neutropenia is the most marked aspect of leukopenia; anemia is normocytic normochromic and often marked; platelet production is often severely affected and the last to recover.

CAUSES OF APLASTIC ANEMIA

Congenital: Fanconl's anemia

Acquired:

1. *Idiopathic or primary aplastic anemia:* cause unknown, may be due to autoimmune process.
2. *Secondary aplastic anemia* due to following causes:
   - Chemicals e.g. benzene
   - Drugs e.g. sulfonamides, chloramphenicol, penicillamine, phenylbutazone, antithyroid drugs, antiepileptic drugs, azathioprine, chemotherapy.
   - Insecticides.
   - Ionizing radiation
   - Infections e.g. viral hepatitis, tuberculosis, EBV, HIV
   - Pregnancy
   - SLE
   - Paroxysmal nocturnal hemoglobinuria

CLINICAL FEATURES

- Anemia – due to low RBC count.
- Infection – due to low WBC count
- Bleeding – due to low platelet count
- Fatigue, pallor, dyspnoea due to anemia
- Persistent minor infections e.g. fungal infection of mouth, sore throat and fever – due to low WBC count.
- Petechiae & ecchymosis – bleeding disorders due to low platelet count.

History

Ask about exposure to drugs, chemicals and radiation

Ask about viral infection e.g. hepatitis

INVESTIGATIONS

Blood CP

Pancytopenia

- Virtual absence of reticulocytes
- Anemia is normocytic normochromic type
- Platelet count is very low
- Leucopenia – specially marked neutropenia

Bone marrow biopsy

Shows a hypocellular or aplastic bone marrow with increased fat spaces.

DIFFERENTIAL DIAGNOSIS

Pancytopenia due to aplastic anemia should be differentiated from pancytopenia due to other causes.

Causes of pancytopenia

- Aplastic anemia
- Megaloblastic anemia
- Bone marrow infiltration or replacement
- Hodgkin's and non-Hodgkin's lymphoma
- Acute leukemia
- Multiple myeloma
- Secondary carcinoma
- Myelofibrosis
- Hypersplenism
- SLE
- Disseminated tuberculosis
- Paroxysmal nocturnal haemoglobinuria
- Overwhelming sepsis

MANAGEMENT

1. Supportive measures

- Packed cell volume and platelet transfusion for bleeding
- Vigorous antibiotics for infection.
- Severe aplastic anemia is defined by the presence of neutrophils less than 500/μL, platelets less than 20000/ μL, reticulocyte count less than 1% and bone marrow cellularity less than 20%.

2. Bone marrow transplantation

It is the treatment of choice for patients under 30 years of age who have HLA – identical donor.

Older patients up to age 45 years may be treated with bone marrow transplantation if there is HLA-matched sibling otherwise treatment is immunosuppressive therapy. Patients more than 45 years are not eligible for bone marrow transplantation because of high risk of graft-versus-host reaction.

3. Immunosuppressive therapy

it is used for those patients who are not suitable for bone marrow transplantation. Anti-thymocyte globuilin plus cyclosporine in combination of corticosteroids. Response usually occurs in 4-12 weeks, but usually partial; however blood counts increase enough to give patients a safe and transfusion free life. Cyclophosphomide should be considered for resistant cases.

4. Treatment to stimulate hemopoiesis

Androgenic steroids are sometimes used in patients not responding to immunosuppressive therapy and in those patients with moderately severe aplastic anemia.

PROGNOSIS

The prognosis of severe aplastic anemia managed with supportive therapy alone is poor and more than 50% patients die within one year. However survival of over 80% has been reported after bone marrow transplantation in young patients and 60% results can be achieved with immunosuppressive regimen involving antithymocyte globulin.

HEMOLYTIC ANEMIA

Hemolytic anemias are caused by increased destruction of red cells. Shortening of red cell survival stimulates bone marrow to compensatory increase in red cell production manifested as reticulocytosis and erythroid hyperplasia. If red cell loss is more than bone marrow capacity, anemia manifests.

Mechanism of hemolysis

- *Abnormalities of the red-cell membrane* e.g. in hereditary spherocytosis. Red cells lose their membrane & become spherocytes which can not pass through reticuloendothelial system of spleen with ease and are sequestered here.
- *Abnormal hemoglobin* e.g. in sickle cell anemia and thalassemia cells are less deformable than normal & are consequently sequestered in spleen.
- *Abnormalities of vessel wall*: In these conditions capillary & vessel walls are abnormal & the fragile red cells can be damaged easily e.g. in DIC.

SITES OF HEMOLYSIS

Intravascular hemolysis

When red cells are rapidly destroyed within the circulation, hemoglobin is liberated into the plasma where it is bound mainly by haptoglobin to form a complex which is taken up by the liver and degraded. It is large complex and cannot be lost in urine.

Any remaining hemoglobin circulates partly as free hemoglobin and mostly bound to albumin to form methemalbumin

If all the haptoglobin has been consumed, free hemoglobin may be lost in the urine. In small amounts it is reabsorbed by the renal tubules where the hemoglobin is degraded and iron is stored as hemosiderin. Sloughing of the renal tubular cells gives rise to hemosiderinuria, which if found always indicates intravascular hemolysis. When greater amounts of hemoglobin are lost, hemoglobinuria occurs, giving the urine a black appearance (black-water appearance).

Evidence of intravascular hemolysis

- Raised level of plasma hemoglobin (hemoglobinemia)
- Hemoglobinuria or hemosiderinuria.
- Very low or absent heptolglobins.
- Presence of methemalbimin – positive Schuman's test (methemalbuminemia).

Causes of intravascular hemolysis

- Falciparum malaria
- Transfusion reaction
- Microangiopathy

Extravascular hemolysis

Here the red cells are removed from the circulation by macrophage in the reticuloendothelial system, particularly the liver and spleen. When the hemolysis occurs chronically it may lead to hypertrophy of the organs involved which may become palpable (such as splenomegaly). There may be little or no depletion of hepatoglobin.

EVIDENCE FOR HEMOLYSIS

Increase red cell breakdown leads to

- Decreased heptoglobins
- Increased plasma hemoglobin
- Haemoglobinuria
- Haemosiderinuria (in chrinic haemolysis)
- Elevated serum unconjugated bilirubin
- Excess urinary urobilinogen (resulting from bilirubin breakdown in the intestine).

Increased red cell production leads to

- Reticulocytosis
- Erythroid hyperplasia of bone marrow
- Skeletal deformities due to marrow expansion such as thickening of vault of skull and widening of marrow cavities and thinning of cortex in tubular bones of extremities.

Other associated effects

- Work hypertrophy of spleen due to congestion
- Increased uric acid production (due to RBC's destruction).

CASES OF HEMOLYTIC ANEMIA

Congenital

Red cell membrane defect

- Hereditary spherocytosis
- Hereditary elliptocytosis

Hemoglobin abnormalities

- Thalassemia
- Sickle cell disease

Metabolic defects

Glucose-6 phosphate dehydrogenase deficiency

Acquired

Immune

1. *Alloimmune*
   - Hemolytic transfusion reaction
   - Hemolytic disease of new born
   - After transplantation.
2. *Autoimmune(causes discussed later)*
   - Warm antibody
   - Cold antibody
3. *Drug induced*

Non-immune

- Mechanical
  Microangiopathic
  March hemoglbinuria
  Burn
  Prosthetic valves
- Infections: malaria, sepsis
- Hypersplenism
- Drugs and chemicals
- Paroxysmal nocturnal hemoglobinuria
- Systemic disease e.g. renal or liver failure.

INHERITED HEMOLYTIC ANEMIAS

- Hereditary spherocytosis
- Hereditary elliptocytosis
- Thalassemia
- Sickle cell disease
- Glucose –6- phosphonate dehydrogenase deficiency

HEREDITARY SPHEROCYTOSIS

It is an autosomal dominant disease characterized by an inherited defect in red cell membrane that makes them spherical, less deformable and vulnerable to splenic sequestration and destruction It is often diagnosed in childhood, milder cases may be discovered incidentally late in adult life.

Clinical features

- Asymptomatic (due to compensatory increased bone marrow function) to severe anemia (aplastic crises) when bone marrow is temporarily impaired by infection.
- Jaundice in episodes. Jaundice may be at birth or delayed for many years.
- Spleen often palpable due to congestion
- *Hemolytic crises* – episodes of increased hemolysis with jaundice, splenomegaly and anemia.
- *Aplastic crises*: complete cessation of marrow function after infection particularly parvovirus.
- *Megaloblastic crises*: due to folic acid deficiency due to increased consumption as a result of hyperactivity of bone marrow.
- There is liability to form pigment gallstones due to chronic hemolysis.
- Leg ulcers sometimes occur.

Investigations

1. Anemia – mild
2. Blood film shows spherocytosis & reticulocytes.
3. Serum bilirubin & urinary urobilinogen are raised – (evidence of hemolysis)
4. ***Osmotic fragility test:*** When red cells are placed in solution of increasing hypotonicity they take in water, swell and eventually lyse. Spherocytosis rupture early than normal cells due to defect in the cell membrane.

Management

1. Splenectomy (because spleen is the site of cell destruction) indicated in the following conditions:
   - Anemia causes persistent impairment of health
   - Severe hemolytic crises
   - Presence of gallstones
2. In hemolytic crises: Blood transfusion
3. Folic acid 5mg daily for indefinite period.

HEREDITARY ELLIPTOCYTOSIS

This disorder of red cell membrane is inherited in an autosomal dominant manner. RBCs are elliptical due to abnormality of spectrin protein. Clinically it is similar to spherocytosis but milder.

THALASSEMIA

It is a group of genetic disorder of hemoglobin synthesis characterized by a decreased synthesis of globin chain.

PATHOPHYSIOLOGY

Two alpha & two beta chains of globin polypeptide combine with haem to form hemoglobin. Therefore if synthesis of globin is reduced it will lead to decreased hemoglobin synthesis and eventually causing microcytic hypochromic anemia.

- Normal adult hemoglobin is primarily hemoglobin A, which represents approximately 98% of circulating hemoglobin. Hemoglobin A is formed from 2 alpha and 2 beta chains ($\alpha2\beta2$).
- Combination of 2 alpha and 2 sigma ($\alpha2\delta2$) forms hemoglobin A2.
- Combination of 2 alpha and 2 gamma ($\alpha2\gamma2$) forms hemoglobin F which is a major form of hemoglobin in fetal life but comprises < 1% of adult hemoglobin.

➢ In beta-thalassemia there is decreased or absent hemoglobin A while hemoglobin F and hemoglobin A2 is increased.

TYPES OF THALASSEMIA

1. Beta thalassemia: If the beta globin chain synthesis is reduced. Beta thalassemia is more common.
2. Alpha thalassemia: If the alpha globin chain synthesis is reduced.

BETA THALLASEMIA

PATHOGENESIS

Each individual has 2 beta polypeptide chain genes situated on homologous chromosomes, one inherited from the mother and one from the father.

- In normal (homozygote) both beta polypeptide genes are normal & produce normal beta polypeptide chains to normal quantity.
- In heterozygote – one gene is normal and other is abnormal (thalassemic) which does not produce beta polypeptide chain. Such condition is called beta thalassemia minor. In such a person normal gene produces enough beta chain to maintain hemoglobin level about normal.
- In abnormal homozygote – both beta chain genes are abnormal (thalassemic) and do not produce beta polypeptide chain. Such condition is called beta thalassemia major.

Decreased beta chain results in unbalanced polypeptide chain production. Beta chain production is impaired or stopped, while alpha chain production is normal. Alpha chain will combine with any beta chains available, while remaining alpha chains combine with gamma chains to form hemoglobin F (fetal hemoglobin).

The free alpha chains precipitate within the red cells resulting in damage of the cell membrane & making them susceptible to phagocytosis by the reticuloendothelial system.

TYPES OF BETA THALASSEMIA			
	Hb A	Hb A_2	Hb F
Normal	97-99%	1-2%	<1%
Thallasemia major	0%	4-10%	90-96%
Thalassemia intermedia	0-30%	0-10%	6-100%
Thalassemia minor	80-95%	4-8%	1-5%

CLINICAL FEATURES

Beta-thalassemia major (Cooley's anemia)

Children affected by beta-thalassemia major present during first year of life with severe anemia requiring transfusion. Signs of thalassemia typically develop after 6 months of age because this is the time when hemoglobin synthesis switches from hemoglobin F to hemoglobin A.

Other problems in thalassemic patients are:

- Growth retardation
- Intermittent infection
- Severe anemia
- Bone marrow hyperplasia causing bossing of head and prominent malar eminence.
- Spinomegaly (early)
- Hepatomegaly (slow to develop)
- Multiple transfusions cause iron overload (hemochromatosis) that results in cirrhosis, cardiac failure and endocrinopathies (usually after transfusion of 100 units).
- Death from cardiac failure (as a result of hemochormatosis) usually occurs between ages 20-30.

Beta thalessemia interemdia

Beta thalassemia is more severe than thalasemia minor but milder than thalassemia major. These patients are those who are symptomatic with moderate anemia (Hb 7-10 g/dl). have milder form of beta thalassemia, allowing a higher rate of globin synthesis. They have chronic hemolytic anemia but do not require transfusion except under period of severe stress. They survive into adult life but with hepatoslenomegaly and bone deformities. Recurrent leg ulcers, gallstones and infection are seen. Hemoglobin electrophoresis shows reduced Hb A while HB A2 and HB F are elevated.

Beta-thalassemia minor

It is asymptomatic, often detected only when there is microcytic anemia on blood CP that does not respond to iron therapy. Then hemoglobin electrophoresis is performed that shows thalassemia minor (raised Hb A2 and often raised HB F).

INVESTIGATIONS

Beta thalassemia major

- Severe microcytic hypochromic anemia.
- Peripheral film is bizarre showing severe microcytosis, hypochromia, poikilocytosis and basophilic stippling.
- Hemoglobin electrophoresis: shows major portion of fetal hemoglobin (HbF) and marked reduction or absent adult hemoglobin (HbA) with variable amount of Hb A2.
- X-ray of skull: shows "hair-on-end" appearance.

Beta thalassemia minor

- Microcytic hypochromic anemia.
- Hemoglobin electrophoresis usually shows a raised Hb A2 (4-8%) and often a raised Hb F (1-5%)

MANAGEMENT

Patients with thalassemia major are treated with:

- Blood transfusion regularly (every 4-6 weeks) to keep the hemoglobin above 10g/dl.
- Folic acid supplements.
- Splnectomy – if hypersplenism causes a marked increase in transfusion requirement.
- Inj. Desferoxamine as a 12-h infusion: It is an iron chelating agent which prevents iron overload due to repeated blood transfusion. Iron overload causes hemochromatosis that can damage endocrine glands, liver, pancreas and myocardium.
- Allogenic bone marrow transplantation for beta thalassemia major with long term survival in more than 80% of cases. The candidates of bone marrow transplantauion are children who have not yet developed iron overload.

Patients with thalassemia intermedia occasionally require transfusion while patients with thalassemia minor require no treatment.

ALPHA THALESSEMIA

Alpha thalassemia occurs due to reduction or absence of alpha chain synthesis.

There are four alpha genes.

- If one gene is deleted, there is no clinical effect.
- If two genes are deleted (alpha thalassemia minor or trait), there is micrycytosis with or without mild anemia.
- If three genes are deleted the patient has hemoglobin H disease (HbH is functionally useless). There is moderate anemia & splenomegaly.
- If all four genes are detected there is no alpha chain synthesis and only Hb Barts is present that canot carry oxygen. Infants are either stillborn at 28-40 weeks or die very shortly after birth. They are pale, edematous and enormous liver and spleen—a condition called ***hydrops fetalis.***

INVESTIGATIONS

Alpha thalassemia minor (trait)

- Mild microcytic hypochrmic anemia.
- *Hemoglobin electrophoresis* shows no increase in percentage of Hb A2 or Hb F, there is no Hb H. Therefore alpha thalassemia is usually diagnosed by exclusion.

Hemoglobin H disease

- Microcytic hypochromic anemia of variable severity.
- Hemoglobin electrophoresis shows presence of Hb H that comprises 10-40% of hemoglobin.

MANAGEMENT

- Alpha thalassemia trait patients require no treatment.
- Patients with hemoglobin H disease should take folic acid and avoid oxidative drugs such as sulfonamides.

SICKLE CELL DISEASE

It is an autosomal recessive disorder resulting from the presence of structurally abnormal hemoglobin (hemoglobin S) in the RBCs which crystallizes on decreased oxygen tension (i.e. on deoxygenation) and dehydration giving shape the RBC as sickle. These cells are rigid and vulnerable to destruction in spleen, resulting in anemia.

PATHOGENESIS

- Hemoglobin S is formed due to hereditary substitution of valine amino acid for glutamine amino acid at the sixth position of the beta chain of hemoglobin.
- To compensate anemia, hypercellularity of marrow occurs that may lead to expansion of marrow cavities producing bossing of the skull, prominent malar bones and protuberant teeth.
- There is an abnormal charge on the sickle cell surface that increases adherence of these cells to endothelium, therefore occluding the vessel and impeding the blood flow.
- Moderate splenomegaly produced by congestion with sickled-red cell results in spleen infarction. Spleen becomes shrunken & fibrotic due to repeated infarctions called "**autosplenectomy**"

CLINICAL FEATURES

This condition usually presents in first year of life when hemoglobin F levels fall and hemoglobin switches from (γ-globin to (β-globin production.

There are two major problems in this condition.

- Hemolytic anemia
- Tissue infarction resulting from vaso-occlusion due to sickled red cells.

Hemolytic anemia

Long- term problems:

- Fatigue
- Increased susceptibility to infection particularly to streptococcus pneumoniae that may cause meningitis or pneumonia. Salmonella or staphylococcus infection may cause osteomyelitis due to increased susceptibility due to repeated ischemic necrosis.
- Chronic leg ulcers: due to ischemia
- Gallstones: Pigment stones from persistent hemolysis & release of bilirubin.
- Aseptic necrosis of bone: particularly of femoral head.
- Blindness: due to retinal detachment or proliferative retinopathy.
- Chronic renal disease
- *Bossing of skull:* due to compensatory hyperplasia of bone marrow in first year of life.

Acute hemolytic crises

In acute form severe anemia occurs as a result of:

- Hemolytic crises that is episode of increased sequestration of sickled cells in spleen (in childhood before the spleen has been infracted as a result of repeated sickling).
- Aplastic crises: bone marrow becomes unable to compensate rapid loss of RBCs due to viral infection of folic acid deficiency.

Infarctions

It is characterized by episodes of severe pain most commonly in bones and spleen but other organs may be involved. It results from vaso-occlusion due to sickled red cells and precipitated by *infection, dehydration and hypoxia.* Clusters of sickled red cells occlude the microvasculature of the organs involved. These episodes last hours to days and produce acute pain and low grade fever.

Bone pain:

Commonest problem. In infants mostly affecting fingers and toes causing painful swelling (*hand-and-foot syndrome*). In adults aseptic necrosis of head of femur is a disabling complication. Other bones are bones of back and chest.

Spleen

Painful infarction of spleen.

Kidney

Papillary necrosis causing renal tubular concentrating defects and gross hematuria (more common in sickle cell trait than in sickle cell disease).

Mesentery:

Mesenteric infarction causes acute abdominal pain.

Chest pain

Chest pain may occur due to bone involvement or pulmonary infarction. Precipitating factors include dehydration, chilling and infection. Pain is excruciatingly severe. Fever, increasing jaundice and malaise are frequent.

CNS

Stroke may occur due to sinus thrombosis.

Penile involvement

Veno-occlusion may lead to priapism.

Other features

- Delayed puberty
- Jaundice
- Hepatomegaly but no splenomagaly in adults.
- Non-healing ulcers of lower leg and retinopathy may be present.

INVESTIGATIONS

Blood CP

- Low hemoglobin, hematocrit usually 20-30%
- High reticulocyte count (usually 10-25%)
- Sickled cells comprising 5-50% of red cells.
- WBC and platelets elevated.

Serum bilirubin

Indirect biliburin level is high.

Hemoglobin electrophoresis

Hemoglobin electrophoresis demonstrates 85-98% hemoglobin S, there is no hemoglobin A, level of hemoglobin F is variable. High hemoglobin F is associated with more benign clinical course.

	Hb A	Hb S	Hb A2	Hb F
Normal	97-99%	0	1-2%	<1%
Sickle cell anemia	0	86-98%	1-3%	5-15%

MANAGEMENT

Allogenic bone marrow transplantation

No curative treatment other than bone marrow transplantation in young patient. Children and adolescents younger than 16 years of age who have severe complications (strokes, recurrent chest syndrome or refractory pain) and HLA- matched donor are the best candidates for transplantation.

Hydroxyurea

This cytotoxic drug that increases the level of hemoglobin F. Hydroxyurea 500-750 mg/d reduces the frequency of painful crises and is now indicated in those patients whose quality of life is disrupted by frequent pain crises.

Supportive measures

- Folic acid 5 mg daily to support the greatly increased RBC production as a compensatory mechanism.
- Treat & prevent infection which causes exacerbation of chronic anemia.
- Avoid precipitating factors e.g. dehydration hypoxia (at high altitudes).
- In hemolytic crises: IV fluids, oxygen, antibiotics, analgesic and if severe anemia blood transfusion.
- For pain: powerful addictive analgesics.

Regular transfusions

Regular transfusions are given only if there is severe anemia or if patients are having frequent crises in order to suppress the production of hemoglobin S. Before elective surgery and during pregnancy, repeated transfusions may be used to reduce the proportion of circulating hemoglobin S to less than 20% to prevent sickling.

Exchange transfusion

Acute vaso-occlusive crises causing severe pain, priapism and stroke can be treated with exchange transfusion.

PROGNOSIS

With standard medical care about 15% die by the age of 20 years and 50% die by the age of 40 years.

SICKLE-CELL TRAIT

Patient with less than 40% hemoglobin S have no symptoms unless they are subjected to anoxia e.g. during anesthesia, this condition is called sickle cell trait. No treatment is required, genetic counseling is recommended.

GLUCOSE – 6 PHOSPHATE DEHYDROGENASE DEFICIENCY ANEMIA

G6PD deficiency is an X-linked recessive disorder affecting 10-15% males, female carriers are rarely affected.

Pathogenesis

Glucose – 6 – phosphate dehydrogenase (G6PD) is the first enzyme in the hexose monophosphate shunt from which red cells derive their metabolic energy, there is also generation of reduced glutathione by this shunt which protects hemoglobin from oxidative denaturation. If this enzyme is deficient it causes episodic hemolytic anemia because the red cells become unable to deal with oxidative stresses. The degree of deficiency of enzyme is more marked in older cells while the young red cells newly produced by bone marrow have normal enzyme activity. Oxidized hemoglobin denatures and form precipitants called Heinz bodies that damages RBC membrane, and these defected RBCs are removed by spleen resulting in hemolytic anemia. Hemoglobin level may fall rapidly and death may occur if patient is not transfused urgently.

Clinical features

Patients are usually healthy without chronic hemolytic anemia or splenomegaly. Hemolysis occurs as a result of oxidative stress on red cells either by infection or exposure to certain drugs. Common drugs initiating hemolysis are dapsone, primaquine, quinine, quinidine, sulfonamide and nitrofurantoin.

G6PD deficiency may present in different ways as following:

- Acute drug – induced hemolysis or after infection.
- Favism (hemolysis after ingestion of feva beans).
- Chronic hemolytic anemia (in severe deficiency of enzyme).
- Neonatal jaundice.

Investigations

- In between hemolytic episodes blood count is normal.
- During episodes of hemolysis, there is reticulocytosis and increased serum unconjugated bilirubin. Red blood cell smear may show " bite cells" the cells that appear to have had a bite taken out of their periphery. This indicates pitting og hemoglobin aggregates by spleen.
- *Heinz bodies* may be demonstrated by staining a peripheral blood smear with crystal violet.
- *G6PD level is low.* However it may be normal if performed shortly after hemolytic episode (because oldest cells with least G6PD activity are destroyed selectively), a second test should be performed weeks after hemolysis.

Treatment

- No treatment, just supportive measures such as transfusion of red cells in severe anemia.
- Avoidance of known oxidant drugs.
- Underlying infection should be treated.
- Splenectomy is not usually helpful.

End of inherited hemolytic anemias, now we will discuss acquired hemolytic anemia.

ACQUIRED HEMOLYTIC ANEMIAS

TYPES

1. **Immune destruction** of red cells by antibodies:
   - *Autoimmune:* warm and cold autoimmune hemolytic anemia.
   - *Alloimmune:* hemolytic transfusion reaction and hemolytic disease of newborn.
   - Drug induced immune hemolytic anemia.
2. **Non-immune** destruction of red cells due to acquired membrane defects e.g. paroxysmal nocturnal hemoglobinuria, microangiopathic hemolytic anemia, valve prosthesis, march hemoglobinuria and secondary to liver or renal disease.
3. **Miscellaneous:** RBC lysis in malaria, mycoplasma, sepsis, hypersplenism & burns.

AUTOIMMUNE HEMOLYTIC ANEMIA

It is an acquired disorder resulting from increased red cell destruction because the body produces antibodies against its own cells. Antibodies bind to the patient's red cells. These anemias are characterized by presence of positive direct antiglobulin (Coomb's) test.
Autoimmune hemolytic anemias are divided into "warm" or "Cold" types depending on whether the antibody attaches better to the red cells at body temperature or at lower temperature.

Warm autoimmune hemolytic anemias

These anemias may occur at all ages especially in middle aged women, presenting as short episodes of anemia and jaundice; spleen is often palpable.

Causes

- Idiopathic
- Autoimmune disorders e.g. SLE
- Lymphomas
- Chronic lymphocytic leukemia
- Carcinomas
- Drugs e.g. methyldopa.

Investigations

- Evidence of *hemolysis* (reticulocytosis, raised unconjugated bilirubin, immature red cells).
- *Coomb's test* is positive with IgG or complement.
- *Spherocytosis* due to red cell damage.
- Autoimmune thrombocytopenia may also present (approximately 10% of patients with autoimmune hemolytic anemia have coincident immune thrombocytopenia; this is called ***Evan's syndrome).***

Treatment

- *Steroids* such as prednisilone 1mg/kg induces remission in about 80% of cases.
- *Splenectomy* may be required if prednisolone is ineffective.
- High dose *intravenous immunoglobulin* (1g daily for 1-2 days) may be highly effective for controlling hemolysis.
- *Immunosuppreesive drugs* such as azathioprine and cyclophosphomide may be effective in patients not responding to steroids and splenectomy.

Cold autoimmune hemolytic anemia

At low temperature IgM cold agglutinin antibodies attach to red cells and cause their agglutination in cold peripheries of the body. In addition activation of complement may cause intravascular hemolysis when the cells return to the higher temperature in the core of the body.

Causes

Idiopathic, lymphomas, paroxysmal cold hemoglobinuria and infections such as mycoplasma pneumoniae, infectious mononeucleosis.

Investigations

- Red cells agglutinate in cold or at room temperature that is reversible after rewarming the sample.
- Coomb's test is positive with complement only.
- Monoclonal IgM antibodies.

Treatment

- Treatment of underlying cause
- Avoid exposure to cold.

ALLOIMMUNE HEMOLYTIC ANEMIA

Antibodies produced in one individual react with the red cells of another. This situation occurs in hemolytic disease of newborn, hemolytic transfusion reaction and after allogenic bone marrow transplantation.

Hemolytic disease of newborn (erythroblastosis fetalis)

This disease results from fetomaternal incompatibility for red cell antigens. Maternal antibodies against fetal red cell antigens pass from maternal circulation via placenta into the fetus, where they destroy the fetal red cells. Only IgG antibodies can cross placenta.

Most common fetomaternal incompatibility is due to ABO incompatibility, where the mother is usually group O and the fetus group A. This disease is mild and exchange transfusion is rarely required.
Another fetomaternal incompatibility is due RhD incompatibility. If an RhD – negative mother carries a RhD - positive fetus, she may develop antibodies against RhD when fetal red cells enter

her circulation during small fetomaternal bleeding episodes in the early third trimester or during delivery or abortion. These antibodies once produced remain in the mother's circulation and poses threat of hemolytic disease for subsequent RhD- positive fetus.

Clinical features

- Clinical features vary from mild hemolytic anemia of newborn to intrauterine death from 18 weeks' gestation with hydrops fetalis.
- Kernicterus occurs due to severe jaundice in the neonatal period, resulting in deposition of unconjugated bilirubin and bile pigments in basal ganglia causing permanent brain damage, choreoathetosis and spasticity. In mild cases it may present as deafness.
- Jaundice

Investigations

Routine antenatal serology

- *ABO and Rh group* and atypical antibodies.
- *Red cell antibodies:* if present, then follow monthly, if titer of IgG is rising or there is previous history of hemolytic disease of newborn aminocentesis is performed to assess the bilirubin level in the amniotic fluid. Fetal blood sampling may be required.

Ultrasound

Ultrasound shows changes in fetal blood flow due to compensated anemia.

Infant sample at birth

A sample of cord from an affected infants shows:

- Anemia with high reticulocyte count.
- Positive direct Coomb's test.
- Raised serum bilirubin.

Treatment

Management of baby

- Mild cases: phototherapy converts bilirubin to biliverdin that is excreted from kidneys reducing the risk of kernicterus.
- Moderate to severe cases: exchange transfusion to replace infant's red cells and to remove bilirubin.

Prevention of RhD immunization in the mother

Passive immunization against hemolytic disease of newborn is achieved with RhD immune globulin (concentrate of antibodies against RhD antigen) 300μg IM is given to mother within 72 hours after delivery or abortion. The antibodies in the immune globulin destroy fetal RhD- positive cells so that mother will not produce anti- RhD antibodies and hemolytic disease in the next RhD – positive fetus may be prevented. One injection of immune globulin is also given at 28th week of pregnancy.

For RhD immune globulin given after delivery it should be assured that:

- Mother is RhD negative.
- Fetus is RhD positive.
- No anti-RhD antibodies in mother's serum i.e. the mother is not previously immunized.

COMPLICATIONS OF TRANSFUSION REACTION

- Immediate hemolytic transfusion reaction presenting as shivering, restlessness, nausea, vomiting, precordial and lumber pain.. Pulse & respiratory rate increase. B.P. falls & patient passes into shock → oliguria →renal failure due to acute tubular necrosis
- Delayed hemolytic transfusion reaction.
- Non- hemolytic febrile reaction.
- Urticaria and anaphylactic reaction.
- Transmission of infection:
  HAV, HBV, HCV, HIV, CMV, EBV, HTLV.
  Malaria, trypanosomiasis, toxoplasmosis
  Bacteria
- Volume overload—pulmonary edema.
- Iron overload
- Massive transfusion of stored blood may cause bleeding and electrolyte changes.
- Thrombophlebitis.
- Air embolism

Management

- Stop transfusion, send again for grouping and cross matching.
- Inj. Hydrocortisone 100mg I/V.
- Antihistamine: Inj. Avil IV
- Diuretics e.g. Inj. mannitol 100ml IV
- Treatment of shock.

Paroxysmal nocturnal hemoglobinuria

Paroxysmal nocturnal hemoglobinuria (PNH) is an acquired clonal stem cell disorder that results in abnormal sensitivity of red cell membrane to lysis by complement. Platelets and granulocytes are also affected and there may be thrombocytopenia and neutropenia.

Clinical features

- *Hemolysis and hemoglobinuria:* Patient reports episodic hemoglobinuria resulting in reddish brown urine as a consequence of hemolysis. Characteristically hemoglobinuria may be present in first morning urine, however in severe case all urine samples are dark.
- *Anemia:* urinary iron loss may be sufficient to cause iron deficiency anemia.
- *Venous thrombosis:* these patients are prone to thrombosis, especially mesenteric and hepatic venous thrombosis. Exact cause of increased predisposion for thrombosis is not known; it may be due to complement- mediated activation of platelets deficient in CD 55 and CD59.
- *Progression*: this disorder is stem cell disorder, therefore can progress to aplastic anemia, myelodysplasia or acute myelogenous leukemia.

Investigations

- Evidence of intravascular hemolysis (finding of urine hemosiderin)
- Serum LDH is characteristically high.
- Iron deficiency anemia.
- WBC and platelets count may be decreased.
- Bone marrow may be hypoplastic or erythroid hyperplasia.
- Flow cytometric assays: confirms the diagnosis by demonstrating the absence of CD59.

Treatment

- No specific treatment, just supportive measures.
- Iron replacement.
- Leukocyte – depleted blood should be used for transfusion to prevent transfusion reactions.
- Steroids (prednisolone) decreases hemolysis.
- Long term anticoagulation for patients with recurrent thromboembolic episodes.
- In patients with bone marrow failure immunosuppressive therapy with antithymocyte globulin or cyclosporin or bone marrow transplantation.

Microangiopathic hemolytic anemia

It is a group of disorders in which red cell fragmentation takes place. The anemia is intravascular, producing hemoglobinemia, hemoglobinuria, and methemalbuminemia. The hallmark of disorder is the finding of fragmented RBCs (called schistocytes or helmet cells) on peripheral blood film.

Causes

- Thrombotic thrombocytopenic purpura (TTP).
- Hemolytic uremic syndrome (HUS).
- DIC
- Hemolysis due to malfunctioning cardiac valve prosthesis
- Metastatic adenocarcinoma.
- Vasculitis.

March hemoglobinuria

There is damage to red cells in the feet associated with prolonged marching or running.

LEUKEMIA

Leukemia are a group of malignant disorders of the hemopoietic tissues characteristically associated with increased numbers of primitive white cells (blast cells) in the bone marrow. These cells proliferate in an uncontrolled fashion and replace normal bone marrow elements.

CLASSIFICATION

Acute leukemia

- Acute lymphoblastic leukemia
- Acute myelogenous leukemia

Chronic leukemia

- Chronic lymphocytic leukemia
- Chronic myeloid leukemia

The terms 'acute' and 'chronic' refer to the clinical behavior of the disease. In acute leukemias the history is usually brief and life expectancy, without treatment, is short. In chronic leukemias the patient has been unwell for years, and survival is long (in years).

Not all leukemias are associated with an increased leukocyte count or even appearance of abnormal cells in the blood.

- <u>*Subluekemic leukemia:*</u> this term is used when the leukocyte count is within or below normal limits but abnormal cells (blasts) are seen in the blood.
- <u>*Aleukemic leukemia:*</u> this term is used when there are no abnormal cells (blasts) to be seen in the blood and the leukocyte count is normal or subnormal. The diagnosis is made from the bone marrow biopsy.

Leukemoid reaction

In some infections there is severe leukocytosis giving the impression of leukemia (e.g. TLC 40,000 or more) with a number of immature cells, this is called leukemoid reaction. It can be differentiated from leukemia by performing Leukocyte Alkaline Phosphatase (LAP score) that is increased in leukemoid reaction (leukocytosis) and decreased in leukemic cells.

ETIOLOGY OF LEUKEMIAS

Exact cause unknown. Following are the risk factors.

RISK FACTORS ASSOCIATED WITH THE DEVELOPMENT OF LEUKAEMIA

Ionizing radiation

A significant increase in myeloid leukaemia followed the atomic bombing of Japanese cities.
An increase in leukaemia was observed after the use of radiotherapy for ankylosing spondylitis and diagnostic radiographs of the fetus in pregnancy.

Cytotoxic drugs

These particularly alkylating agents, may induce myeloid leukaemia, usually after a latent period of several years.

Exposure to benzene in industry

Retroviruses

One rare form of T cell leukaemia/lymphoma appears to be associated with retrovirus similar to the viruses causing leukaemia in cats and cattle.

Genetic

There is a greatly increased incidence of leukaemia in the identical twin of patients with leukaemia.
Increased incidence occurs in Down's syndrome and other genetic disorders.

Immunological

Immune deficiency states are associated with an increase in hematological malignancy.

AGE INCIDENCE

- Acute lymphoblastic leukemia: childhood 1-5 years.
- Acute myelogenous: Adults
- Chronic leukemia: middle & old age.

ACUTE LEUKEMIAS

Acute myelogenous (or myeloid) leukemia (AML) is about 8- times more common than lymphoblastic leukemia (ALL) in adults. In young children lymphoblastic variety is more common.

PATHOLOGY

They have the following characteristic pathological features.

- Failure of maturation
- Proliferation of cells which do not mature leads to an increasing accumulation of useless cells which take up more and more marrow space, suppressing the normal cells from bone marrow resulting in anemia, thrombocytopenia and infection.

  These proliferating cells spill into blood causing widespread infiltration in liver, spleen, lymph nodes and other sites throughout the body.

CLINICAL FEATURES

Symptoms

- *Symptoms of anemia:* Headache, fatigue, faintness, palpitation and breathlessness.
- *Infections:* perianal & skin infection.
- *Hemorrhagic manifestations:* Skin petechiae, bruises, bleeding from gums, nose or persistent bleeding after tooth extraction or tonsillectomy.
- *Bone pain*: especially sternal tenderness
- *Organ infiltration:* Marked gum hypertrophy.

Signs

- Pallor
- Brusing peteciae, bleeding gums & gum hypertrophy
- Lymph adenopathy
- Splenomegaly – Sight to moderate
- Hepatomegaly
- Hemorrhage in the optic fundus

INVESTIGATIONS

1. Blood CP

The hallmark of acute leukemia is combination of pancytopenia with circulating blasts. However blasts may be absent in peripheral blood in about 10% of patients called aleukemic leukemia. Platelet count – decreased.

2. Bone marrow biopsy:

The marrow is hypercellular with replacement of normal elements by leukemic blast cells in varying degree. More than 20% blasts are required for diagnosis of acute leukemia.

3. Other investigations

- Serum uric acid: hyperuricemia
- Serum calcium
- Blood culture
- X-ray chest: patients with lymphoblastic leukemia may have mediastinal mass visible on chest x-ray.
- CSF: meningeal leukemia will have blast cells in CSF in about 5% of cases at diagnosis.

These investigations are done to see tumor lysis syndrome in which rapid destruction of leukaemic cells, liberation of phosphate & other intracellular components result in hyperphosphatemia, hypercalcemia, hyperkalemia and hyperuricemia.

Differentiation between myeloid and lymphoblastic leukemia

<u>*Acute myelogenous leukemia*</u>

The Auer rod, an eosoinphilic needle-like inclusion in cytoplasm of blast cells, is pathgenomic of acute myelogenous leukemia.

To confirm the myeloid nature of the cells, histochemical stains demonstrating myeloid enzymes such as myeloperoxidase may be useful.

<u>*Acute lymphoblastic leukemia*</u>

Diagnosis is confirmed by demonstrating surface markers characteristic of lyphoid cells as following:

Terminal deoxynucleotidal transferase (TdT) is present in 95% cases of acute lymphoblastic leukemia.

MANAGEMENT

- Supportive treatment
- Specific treatment

<u>SUPPORTIVE TREATMENT</u>

1. **Anemia:** blood transfusion (packed cell volume).
2. **Thrombocytopenia:** platelets transfusion.
3. **Infections:** antibiotics.

   Bacterial:

   Antibiotics are given according to the organism isolated from culture; mean while gentamicin + azlocilin is given for 9 days. The organisms most commonly associated with severe neutropenia are gram-negative bacteria such as E, coli, pseudomonas and klebsiella, and gram- positive bacteria such as staphylococcus areus. Patients with lymphoblastic leukemia are suspected to infection with pneumocystis carinii which causes severe pneumonia. Treatment is with high dose cotrimoxazole.

   Fungal:

   - Prophylactic for oral infection nystatin suspension 1ml held in mouth
   - Established infection: nystatin suspension 1ml QID.
   - Systemic infection I/V amphotericin
   - Topical gentian violet paint for severe infection.

   Viral

   Herpes simplex around the mouth & nose is treated with Acyclovir cream applied to the lesion QID OR Tab. Acyclovir 200 mg 5 times / day for 5-10 days.

PREPARATIONS FOR SPECIFIC THERAPY

- Existing infection should be identified and treated (e.g. urinary tract infection, oral candidiasis, dental, gingival and skin infections).
- Anemia corrected with red cell concentrate infusion.
- Thrombocytopenic bleeding controlled with platelet transfusion.
- If possible, insertion of sylastic catheter in to the neck veins for venous access.
- Careful explanation of the therapeutic regimen to the patient.

<u>SPECIFIC TREATMENT</u>

The aim of treatment is to destroy the leukemic clone of cells without destroying the residual normal stem cells. There are three phases of treatment as following:

- Remission induction phase
- Remission consolidation phase
- Remission maintenance phase

1. Remission induction phase

In this phase bulk of the tumor is destroyed by combination chemotherapy. The patients go to periods of marrow hypoplasia requiring intensive supportive therapy.

2. Remission consolidation phase

If remission has been achieved by induction therapy, residual disease is attacked by therapy during this (remission consolidation) phase. This consists of a number of courses of chemotherapy. In acute lymphoblastic leukemia it is necessary to give therapy to the central nervous system (intrathecal methotrexate) along with cranial radiation.

3. Remission maintenance phase

When bulk of tumor is reduced to a minimum, maintenance therapy is given in acute lymphoblastic leukemia for a period of about 2-3 years. This phase is not required in acute myelogenous leukemia.

DRUGS COMMONLY USED IN THE TREATMENT OF ACUTE LEUKEMIA

Phase	Lymphoblastic	Myelogenous
Induction phase	Vincristine IV Prednisolone oral L- asparaginase IV Daunorubicin IV Methotrexate (intrathecal)	Daunorubicin IV Cytarabine IV Etoposide IV oral Tioguanine oral
Consolidation phase	Daunorubicin IV Cytarabine IV Etoposide IV oral Methotrexate IV	Cytarabine IV Amsacrine IV Mitoxantrone IV
Maintenance phase	Prednisolone oral Vincristine IV Mercaptopurine oral Methotrexate oral	

TREATMENT OF RECURRENCE (RELAPSE)

ALL

A proportion of patients are cured with initial therapy. In the rest disease recurs and ultimately proves fatal unless second remission is achieved with chemotherapy and bone marrow transplantation.

Common sites for relapse: Bone marrow, CNS, testis

- Bone marrow relapse – marrow transplantation
- CNS relapse – intrathecal drugs and craniospinal irradiation.
- Testicular relapse – irradiation and re-induction of therapy.

AML

- With modern combination chemotherapy, approximately 70-80% of patients of acute leukemia under age 60 years achieve complete remission.
- However within 1- 3 years disease recurs in at least 60% of patients. In young patients if second remission is achieved cure may be possible with allogenic or autologous bone marrow transplantation.
- Older patients with AML achieve complete remission in up to 50% of cases. In recurrence intensive chemotherapy, antibiotics, blood transfusion and hydroxyurea.

POOR PROGNOSTIC FEATURES IN ACUTE LEUKAEMIA

- Increasing age
- Male sex
- High leukocyte levels at diagnosis
- Cytogenic abnormalities
- CNS involvement at diagnosis

CHRONIC LEUKAEMIAS

CHRONIC MYELOID LEUKAEMIA (CML)

Chronic myeloid leukemia is a myeloproliferative disorder characterized by over production of myeloid cells. These myeloid cells retain the capacity for differentiation, and normal bone marrow function is retained during the early phases.

- Age incidence: 35-80 years. Peak age 55 years
- About 90% of patients with CML have a chromosome abnormality known as Philadelphia (Ph) chromosome. Maturation of cells is normal.

CLINICAL FEATURES

The disease has three phases

- Chronic phase: in this phase disease is responsive to treatment & easily controlled.
- Accelerated phase: Disease control becomes more difficult.
- Blast crisis phase: In this phase the disease transforms from chronic to acute leukemia which is relatively non-responsive to treatment.

Chronic phase

Non- specific features:

Patients usually present with fatigue, night sweats and low- grade fever due to hypermetabolic state caused by overproduction of white cells.

Abdominal fullness:

Patient may present with complain of abdominal fullness due to splenomegaly.

Incidental finding of very high WBC count.

Leukostasis (hyperviscosity syndrome):

Some patients present with a clinical syndrome related to leukostasis due to very high WBC count (usually > 500,000/μL) presenting with blurred vision, respiratory distress, or priapism.

On examination

- Spleen is massively enlarged (in 90%)
- Sternal tenderness due to marrow overexpansion.
- Hepatomegaly in 50%
- Lymphadenopathy (rare)

Accelerated phase

Patients presenting in accelerated phase present with fever in the absence of infection, bone pain, and splenomegaly.

Blast crisis

Patients present with acute leukemia (myeloid in 80% and lymphoid in 20%) manifesting as bone marrow failure resulting in bleeding and infection. Blast crisis is resistant to treatment, the median survival is less than 6 months.

INVESTIGATIONS

Chronic phase

Blood CP:

- The hallmark of CML is an elevated WBC count; median white cell count at diagnosis is 150,000/μL.
- Greatly increased number of neutrophils, metamyelocytes, myelocytes and blast cells.
- Blast cells are usually less than 5%.
- Patient is usually not anemic at diagnosis.
- Platelet count is normal or elevated, sometimes very high, morphology of platelet is normal.
- Basophil or eosinophil count may be elevated.

Bone marrow biopsy:

The bone marrow is hypercellular with left-shifted myelopoiesis. Myeloblasts are less than 5%.

Neutrophil alkaline phosphatase (LAP score)

Neutrophil alkaline phosphatase is low.

Serum vitamin B12

Serum Vit. B12 very high due to increased secretion of transcobalamin III.

Serum uric acid

Serum uric acid level is high.

Philadelphia chromosome

Philadelphia chromosome may be detected in either peripheral blood or bone marrow.

In accelerated and blast phase

There is progressive anemia, thrombocytopenia with increased blast cells in blood and bone marrow.

MANAGEMENT

Treatment is usually not emergent even with WBC count > 200,000/ μL since the majority of circulating cells are mature myeloid cells. Hyperviscosity syndrome requires urgent leukopharesis in conjunction with myelosuppressive therapy.

Imatinib mesylate

- This drug is an inhibitor of tyrosine kinase activity of *bcrlabl* oncogene.
- It is well tolerated and results in hematological control in 98% of patients in chronic phase.
- It has replaced hydroxyurea and interferon as a standard therapy.
- For chronic phase dose is 400 mg orally daily. Side effects are nausea, periorbital swelling, rash, and myalgia.

Hydroxyurea

Hydroxyurea (Hydrea 500mg) was the most widely used oral agent to provide initial control of the disease, however its indication now is in patients who cannot tolerate imitanib. Usual dose is 0.5-2.5 g/day, dose is adjusted to keep the WBC count around 5000/μL. Response is good, WBC count decreases, spleen becomes smaller and symptoms disappear. Interruption in therapy leads to rapid rebound of WBC.

Alpha interferon

Recombinant alpha interferon had largely replaced hydroxyurea as the treatment of choice for CML for chronic phase before the development of imitanib. It prolongs the chronic phase of disease and survival, however it has disadvantage of being given by S/C and marked side effects. The role of this agent is likely to be that of adjunct to imitanib. Dose is 5 million units daily for 5 years. Response requires about 6-18 months), then decide to continue or stop interferon. Interferon is very expensive and has side effects such as flue-like symptoms, weight loss, somnolence, nausea, vomiting, diarrhea and headache.

Bone marrow transplantation

The only curative therapy is allogenic bone marrow transplantation. This treatment is available for adults under age 60 who have HLA- matched sibling. Sixty percent of adults have long term

disease free survival following bone marrow transplantation. The best results are seen in patients who are under 40 and transplanted within 1 year after diagnosis. An alternative approach is to start with imitanib and recommend transplant if there is no cytogenetic response after 6 months.

PROGNOSIS

Average survival period in the past was about 3-4 years. With interferon it increased to 5-6 years. Marked improvement in survival rate is anticipated with imitanib, but this remains to be proved.

CHRONIC LYMPHOCYTIC LEUKAEMIA (CLL)

- This is the commonest variety of leukemia
- Age incidence: above 45 years, peak age 65 years.
- Sex incidence: male to female ratio is 2:1

CLL is a clonal malignancy of B lymphocytes (rarely T lymphocytes). In this disease B lymphocytes fails to form antibodies therefore increasing number of immuno-incompetent cells accumulate, causing impairment of immunity and bone marrow function. Clinical features are related to immunosuppression, bone marrow failure and organ infiltration.

CLINICAL FEATURES

- *Onset* – insidious
- Mostly patients are *asymptomatic* & first time present with lymphadenopathy (in 80% and hepatosplenomegaly (in 50%).
- *Recurrent infections* due to immunosuppression (pneumonia & herpes virus infections).
- *Lymphadenopathy:* Enlarged nodes are non tender, firm, rubbery & discrete found in the cervical, axillary and inguinal regions.
- *Splenomegaly*: Spleen is usually palpable but smaller.
- *Hepatomegaly.*
- Infiltration of serious membranes: results in pleural or pericardial effusion.
- Autoimmune hemolytic anemia or autoimmune thrombocytopenia in 5-10% cases.

INVESTIGATIONS

Blood CP

- *Anemia (mild)*
- *WBC count* is usually more than 20,000/μL in which 75-98% are lymphocytes. Usually lymphocytes appear small and mature and morphologically indistinguishable from normal lymphocytes.
- *Platelet count* usually normal at the time of presentation.

Bone marrow biopsy

Bone marrow is infiltrated with small lymphocytes.

Serum immunoglobulins: low

COURSE OF THE DISEASE

- Most benign of all leukaemias
- Death is usually due to infection from bone marrow failure and immunodeficiency.

> **STAGING OF CHRONIC LYMPHOCYTIC LEUKAEMIA**
>
> **Clinical stage A**
> No anemia or thombocytopenia and less than three areas of lymphoid enlargement.
>
> **Clinical stage B**
> No anemia or thrombocytopenia with three or more involved areas.
>
> **Clinical stage C**
> Anemia and/or thrombocytopenia regardless of the number of areas of lymphoid enlargement.

MANAGEMENT

Stage A:

No specific treatment is required. Life expectancy is normal in older patients.

Stage B:

- If asymptomatic – no treatment
- If symptomatic – fludarabine or chlorambucil & local radiotherapy of lymph node.

Stage C:

- *Anemia:* packed cell volume.
- *Infections:* suitable antibiotics, immunoglobulin replacement may be required..
- *Hemolytic anemia* or thrombocytopenia: Prednisolone or splenectomy.
- *Cytotoxic drugs*: combination of fludarabine and chlorambucil.
- *Allogeneic bone marrow transplantation*: if disease not controlled with cytotoxic drugs.

PROGNOSIS

Average survival period is about 6 years
Stage A – survival over 12 years
Stage C – survival 2-3 years.

HAIRY CELL LEUKEMIA (HCL)

Hairy cell leukemia is a clonal proliferation of B-lymphocytes which accumulate in the bone marrow and spleen.

- Median age at diagnosis:
- Male to female ratio 6:1.

Clinical features

- Symptoms are similar to CLL such as fatigue, recurrent infections.
- Splenomegaly occurs in 90% of cases, it may be massively enlarged.
- Hepatomegaly in 50%
- Lymphadenopathy is uncommon.

Investigations

- Pancytopenia is the hallmark of HCL presenting as anemia, thrombocytopenia and neutropenia.
- Hairy cells are usually present in small numbers on peripheral blood film and have characteristic appearance with numerous cytoplasmic projections.
- Bone marrow: usually dry tap (in-aspirable).

Differential diagnosis

- Other lymphoproliferative disorders such as Waldenstrom's macroglobinemia and hodgkin's lymphoma.
- Other causes of pancytopenia.

Treatment

Cladribine (2- chlorodeoxyadenosine) daily for 7 days causes complete remission in 80% of cases. Remission lasts for several years and patient may be re- treated. Alpha- interferon and the purine analogue deoxycoformycin are also effective.

LYMPHOMAS

The lymphomas are the malignant tumors of lymphoid tissue, characterized by the abnormal proliferation of B or T cells in the lymphoid tissue.

TYPES

There are two histological types:

- Hodgkin's disease
- Non-Hodgkin's disease.

HODGKIN'S DISEASE

It is characterized by aggressive enlargement of lymph nodes (due to hyperplasia, and infiltration with histocytes and lymphocytes) and presence of characteristic Reed-Sternberg cells.

> **PATHOLOGICAL CLASSIFICATION OF HODGKIN'S LYMPHOMA**
> - Lymphocyte predominant
> - Nodular sclerosing
> - Mixed cellularity in which neutrophils, eosinophils and plasma cells are common
> - Lymphocyte depleted.

INCIDENCE

- Age: median age 31 years. First peak in 20-35 and second peak in 50-70 years.
- Sex: Male to female ratio is 1.5:1
- Onset: insidious

CLINICAL FEATURES

An important clinical feature of Hodgkin's disease is it tendency to arise within lymph nodes areas and to spread in an orderly fashion to contiguous areas of lymph nodes.

Local features

Lymphadenopathy: Enlargement of cervical lymph nodes (in 70%), mediastinal lymph nodes (in 60%) sometimes first detected on x-ray chest. Other lymph nodes of axilla, groins, or abdomen may be enlarged.

- The lymph nodes are painless & rubbery
- Characteristic appearance of cervical lymph nodes in advanced cases is pyramidal swelling with its base at the clavicle and its apex at the angel of the jaw.

Splenomegaly uncommon

Systemic features

Majority of patients presenting with Hodgkin's disease have few or no systemic symptoms, however 25-35% of patients have some constitutional symptoms such as:

1. Low grade fewer, which may be associated with recurrent *night sweats*. Pattern of fever may be like Pel-Epstein fever – fever of several weeks duration interrupted by periods of remission.
2. Unexplained weight loss more than 10% over 6 months.
3. Pain at the site of disease after drinking alcohol in 2-5% of patients.
4. Fatigue, weakness and malaise.
5. Symptoms of metastatic growth or infiltrations.
    - Skin: pruritus
    - Bones – localized pain & tenderness
    - Pressure by mediastinal lymph nodes – dyspnoea, cyanosis and strider.
    - Superior vena caval obstruction may be the presenting features.
    - Sudden spinal cord compression is usually a feature of advanced disease.
    - GIT – abdominal pain, ascites
    - Genitourinary – hematuria.

CLINICAL STAGES OF HODGKIN'S DISEASE (Ann Arbor-classification)	
Stage I	Involvement of a single lymph node region (I) or extra lymphatic site (IE)
Stage II	Involvement of two or more lymph node regions (II) or an extralymphatic site and lymph node regions on the same side of (above or below) the diaphragm (IIE)
Stage III	Involvement of lymph node regions on both sides of the diaphragm with (IIIE) or without (III) localized extralymphatic involvement or involvement of the spleen (IIIS) or both (IIISE)
Stage IV	Diffuse involvement of one or more extralymphatic tissues, e.g. liver or bone marrow
Stage A	No systemic (constitutional) symptoms
Stage B	10% weight loss in 6 months, fever, drenching night sweats
	The lymphatic structures are defined as the lymph nodes, spleen, thymus, Waldeyer's ring, appendix and Peyer's patches.

Staging is same for both Hodgkin's disease and non-Hodgkin's lymphoma.

DIFFERENTIAL DIAGNOSIS OF CERVICAL LYMPH NODE ENLARGEMENT

Infections

Acute:

- Pyogenic infections
- Infective mononucleosis
- Toxoplasmosis
- Cytomegalovirus infection
- Infected eczema
- Cat scratch fever
- Acute childhood exanthema

Chronic

- Tuberculosis
- Syphilis
- Sarcoidosis
- HIV infection

Connective tissue disorders

Rheumatoid arthritis

Drug reactions

Phenytoin

Primary lymph node malignancies

- Hodgkin's disease
- Non-Hodgkin's lymphoma
- Chronic lymphocytic leukaemia
- Acute lymphoblastic leukaemia

Secondary malignancies

- Nasopharyngeal
- Thyroid
- Laryngeal
- Lung
- Breast
- Stomach

INVESTIGATIONS

1. **Lymph node biopsy**: percutaneous needle biopsy or excisional biopsy shows Reed – Sternberg cells.
2. **Blood CP/ESR**: normocytic normochromic anemia, raised ESR
3. **X-ray chest** may show mediastinal lymphadenopathy or pulmonary infiltration
4. **CT Scan** of chest and abdomen for staging.
5. **LFTs**: may be abnormal due to hepatic infiltration or obstruction of porta hepatis.
6. **LDH**: raised levels are an adverse prognostic factor.

MANAGEMENT

- **Radiotherapy:** Most effective for localized Hodgkin's disease in stage I & II.
- **Chemotherapy:** combination chemotherapy for patients with disseminated disease.

The ChlVPP regimen

Chlorambucil
6mg/m2 (up to 10mg total) days 1-14 orally

Vinblastine
6mg/m2 (up to 10 mg total) days 1 and 8 i.v.

Procarbazine
100mg/m2 days 1-14 orally

Prednisolone
40 mg/m2 days 1-14 orally

Over 80% patients respond to the above regimen when these drugs are delivered every 3-4 weeks for a total 6-8 cycles. The risk of infertility in male is very high.

THERAPEUTIC GUIDELINES FOR HODGKIN'S LYMPHOMA

Indications for radiotherapy
- Stage I disease
- Stage II A disease with 3 or less areas of involvement
- After chemotherapy to sites where there was originally bulk disease
- To lesions causing serious pressure problems.

Indications for chemotherapy
- All patients with 'B' symptoms
- Stage II disease with more than three areas of involvement.
- Stage III and Stage IV disease.

PROGNOSIS

Over 90% of patients with stage IA are cured by radiotherapy alone. Patients with stage IIA have a reduced cure rate from radiotherapy. Approximately 70% of patients treated with chemotherapy are cured. The 15% of patients who fail to initial chemotherapy have a poor prognosis.

NON-HODGKIN'S LYMPHOMA (NHL)

In this group of disorders there is malignant monoclonal proliferation of lymphoid cells. The lymphoid cells are B-lymphocytes (in 70%) or T lymphocytes (in 30%). The extranodal involvement is common e.g. in tonsils, adenoids, nasopharyngeal glands, gut or skin.

TYPES

- Low grade
- Intermediate grade
- High grade

Subdivision into grades reflects the rate at which the cells are dividing. High-grade lymphomas are potentially curable while low-grade lymphomas are generally considered incurable with conventional therapy.

CLINICAL FEATURES

Non- Hodgkin's lymphoma is widely disseminated at presentation more commonly than Hodgkin's disease, presenting with lymph node enlargement with systemic features. Extranodal involvement is more common in NHL involving bone marrow, gut, thyroid, lung, skin, testes, brain and rarely bone. Bone marrow involvement is more common in low-grade lymphoma (50-60) rather than high grade (10%).

1. **Lymphadenopathy:** Lymph nodes are painless, discrete & firm. Mediastinal lymph node involvement is less common while abdominal nodes are commonly involved. Involvement of Walder's ring, epitrochlear and mesenteric lymph nodes are more frequently observed with NHL than Hodgkin's lymphoma.
2. **Non-specific symptoms**: tiredness, weight loss & fever.
3. **Weakness of legs** progressing to paraplegia may occur due to metastasis to extradural space compressing the spinal cord.
4. **Bone pain**: When there is bone involvement
5. **Hepatosplenomegaly** may occur early in the disease.
6. **Other features:** intestinal obstruction, ascites, and superior vena caval obstruction.

INVESTIGATIONS

- *Lymph node biopsy*
- *Bone marrow aspiration & trephine biopsy* may show infiltration by lymphoid tissue because marrow involvement is common.
- *X-ray chest & CT scan* of abdomen to see lymph node involvement.

TREATMENT

FACTORS DETERMINING MANAGEMENT STRATEGY IN NON-HODGKIN'S LYMPHOMA

- Age of the patient
- Degree of ill health (concomitant disease)
- Histological grade
- Staging of the disease
- HIV status
- Patient's wishes.

Management of low- grade lymphoma

Asymptomatic patients may not require therapy. However disease will progress and require treatment in 1-3 years.

Indications for treatment: marked systemic symptoms, lymphadenopathy causing discomfort or disfigurement, bone marrow failure or compression syndromes. The options are:

- *Radiotherapy:* for localized stage I disease.
- *Chemotherapy*: it is the treatment of choice. Chlorambucil 0.6-1 mg/kg every 3 weeks or combination therapy with cyclophosphomide, vincristine and prednisolone (CVP).

Management of high - grade lymphoma

- *Radiotherapy:* of localized disease.
- *Chemotherapy:* for stage II, III and IV – intensive combination chemotherapy with CHOP regimen including cyclophosphomide, adriamycin, vincristine and prednisolone.
- *Transplantation:* autologous stem cell transplantation appears to benefit some patients at first relapse with cure rate of 50%, compared to <10% with chemotherapy.
- *Monoclonal antibody* (rituximab) therapy with CHOP chemotherapy causes dramatic improvement in survival.

PROGNOSIS

Low-grade NHL

The tumors run an indolent remitting and relapsing course with an overall median survival of 10 years. Death results from transformation into high grade NHL which is associated with poor prognosis.

High – grade NHL

About 80% of patients respond initially but only 35% will have disease – free survival at 5 years. Relapse is associated with poor response to further chemotherapy (< 10% 5-year survival), but in patients under 65, stem cell transplantation improves survival.

Poor prognostic signs

Increasing age, advanced stage, concomitant disease, a raised LDH and T-cell lymphoma are poor prognostic signs.

MYELOPROLIFERATIVE DISORDERS

Myeloproliferative disorders are due to acquired clonal proliferation of bone marrow hematopoietic stem cells. Since the stem cells give rise to myeloid, erythroid, and platelet cells, changes occur in all these cell lines. Majority of patients have one of these disorders, however some have overlapping features. All of the myeloproliferative disorders may progress to acute myelogenous leukemia.

1. Proliferation of erythroid precursors causes polycythemia rubra vera
2. Proliferation of megakaryocytes causes essential thrombocythemia and myelofibrosis.
3. Proliferation ofmyeloid cells causes chronic myeloid leukemia..

Therefore myeloprolifetative disorder includes 4 conditions:

- Polycythemia rubra vera
- Essential thrombocytosis
- Myelofibrosis
- Chronic myeloid leukemia (already discussed in the section of leukemia)

POLYCYTHEMIA VERA

Polcythemia rubra vera is an acquired myeloproliferative disorder that causes overproduction of all three hematopoietic cell lines, most prominently the red blood cells. The hematocrit is elevated and value exceeds 54% in males or 51% in females.

CLINICAL FEATURES

Most patients present with symptoms of expanded blood volume and hyperviscosity such as:

- *Features of hyperviscosity:* headache, dizziness, tinnitus, blurred vision, and fatigue.
- *Features of expanded blood volume;* epistaxis due to engorgement of mucosal blood vessels and qualitative abnormality of platelets.
- *Pruritus following a warm bath:* due to histamine release from increased number of basophils.
- *On examination*: plethora, cyanosis, redness of conjunctiva, engorged retinal vessels, palpable spleen (in 75%) and palpable liver in 50%.

COMPLICATIONS

1. Thrombosis: increased incidence of peptic ulcer and GI bleeding.
2. High incidence of peptic ulcer disease
3. Gout due to high cell turnover.

DIFFERENTIAL DIAGNOSIS

1. **Other myeloproliferative disorders**
2. **Relative polycythemia:** elevated hematocrit due to contracted plasma volume rather than increased red cell mass, usually associated with diuretic use.
3. **Secondary polycythemia:** a secondary cause of polycythemia should be suspected if splenomegaly is absent and high hematocrit is not accompanied by increase in other cell lines. Secondary causes of polycythemia may be:
   - Hypoxia: perform ABGs.
   - Lung diseases: take history of smoking, chest x-ray.
   - Right to left cardiac shunt (perform echo)
   - <u>Inappropriate increase in erythropoietin:</u> renal cell carcinoma, Wilm's tumor, renal cyst, hepatocellular carcinoma, adrenal tumors, cerebellar hemangioblastoma, and massive uterine fibroma.

INVESTIGATIONS

Blood CP

- Increased hematocrit > 54% in males and > 51% in females.
- Hemoglobin is elevated.
- WBC count is elevated to 10,000 – 20,000/μL.
- Platelet count is increased sometimes exceeding 100000/μL, platelet morphology is normal.
- Basophilia and eosinophila are common.

Red cell mass

Red cell mass is elevated > 36 ml/kg in males and 32 ml/kg in females. (Normal values: 26-34 ml/kg in males and 21-29 ml/kg in females)

Bone marrow

Bone marrow is hypercellular, with panhyperplasia. Iron stores are absent.

Arterial blood gases

For hypoxia

Serum erythropoietin

Serum erythropoietin: low in polycythemia vera while in secondary polycythemia it is usually high or normal.

Other tests

- Serum B12 is elevated due to increased secretion of transcobalamin III secreted by WBC.
- Leukocyte alkaline phosphatase is elevated,
- Serum uric acid level is raised.

DIAGNOSIS OF PRIMARY PROLIFERATIVE POLYCYTHAEMIA: POSITIVE FEATURES

- Elevated red cells mass
- Splenomegaly
- An associated elevation of white cell and platelet counts
- Hypercellular marrow with hyperplasia of erythropoiesis/granulopoiesis and megakaryoctes Absent iron stores
- Elevated neutrophil alkaline phosphatase score.
- Elevated serum B12 levels.
- Absence of secondary causes of erythrocytosis
- Serum erythropoietin is low.

TREATMENT

Venesection

Venesection (phlebotomy) one unit of blood (about 500ml) is removed weekly until the hematocrit is less than 45%.

Hydroxyurea

This alkylating agent is required when there is thrombosis, severe pruritus or high phlebotomy requirement. The usual dose is 500-1500mg/d, adjusted to keep platelets below 500000/μL without reducing neutrophil count to less than 2000/μL.

Aspirin

Low dose aspirin decreases the risk of thrombosis.

PROGNOSIS

The median survival after diagnosis in treated patients exceeds 10 years. Some patients survive more than 20 years. The disease may convert into other myeloproliferative disorder such as CML or myelofibrosis.

MYELOFIBROSIS

It is a myeloproliferative disorder characterized by fibrosis of bone marrow, splenomegaly and leukoerythroblastic peripheral blood picture with teardrop poikilocytosis.

Bone marrow fibrosis occurs due to fibroblast-stimulating factors such as platelet – derived growth factor released from abnormal megakaryocytes in the bone marrow. Due to marrow fibrosis, extramedullary hematopoiesis takes place in the liver, spleen and lymph nodes.

Myelofibrosis = bone marrow fibrosis + extramedullary hematopoiesis (blood formation).

CLINICAL FEATURES

Myelofibrosis develops in adults over age 50 and is usually insidious in onset.

Features of bone marrow failure

Patients present initially with fatigue due to anemia, bleeding due to thrombocytopenia or abdominal fullness due to splenomegaly.

Later more bone marrow failure takes place due to progressively more fibrosis leading to anemia and thrombocytopenia.

Features due to extramedullary hematopoiesis

- Spleen becomes massively enlarged due to extramedullary hematopoiesis, painful episodes of splenic infarction may occur.
- Extramedullary hematopoiesis in liver leads to portal hypertension, ascites and esophageal varices.
- Transverse myelitis: if hematopoiesis occurs in epidural space.
- Severe bone pain especially in upper legs.

INVESTIGATIONS

Blood CP

- Anemia with leukoerythroblastic picture (combination of immature RBCs and WBCs). Poikilocytosis with red cells having characteristic teardrop shape.
- WBC count is usually high and may be similar to seen in CML, later leukopenia may occur.
- Platelet count is initially very high, in later stages thrombocytopenia occurs. Platelets may be giant with bizarre morphology.
- The triad of teardrop poikilocytosis, leukoerythroblastic blood picture and giant abnormal platelets is highly suggestive of myelofibrosis.

Bone marrow

Bone marrow is very difficult to aspirate (dry tap). Trephine biopsy shows increased fibrous tissue.

DIFFERENTIAL DIAGNOSIS

- **Leukoerythroblastic picture:** also present in severe infection, inflammation or infiltrative bone marrow processes but there is no teardrop poikilocytosis and giant abnormal platelets.
- **Bone marrow fibrosis:** may also be seen inmetastatic carcinoma, Hodgkin's disease, and hairy cell leukemia.
- **CML:** leukocytosis is accompanied normal RBC morphology and presence of Philadelphia chromosomes.

TREATMENT

- Treatment is supportive with transfusion.
- Folic acid should be given.
- Hydroxyurea is given to reduce spleen size and to reduce very high WBC count.

- Splenectomy may be required in patients with recuurent painful splenic infarctions, severe thrombocytopenia or an acceptable transfusion requirement.
- The disease is progressive, allogeneic bone marrow transplantation has been performed with 50% long-term survival and should be considered in young patients.

ESSENTIAL THROMBOCYTOSIS

Essential thrombocytosis is a an uncommon myeloproliferative disorder of unknown cause in which marked proliferation of megakaryocytes in the bone marrow leads to elevation of the platelet count.

CLINICAL FEATURES

- The median age at presentation 50-60 years.
- Slightly more common in females.
- Patient may be diagnosed incidently when blood CP shows very high level of platelets.
- The most important clinical problem is thrombosis. Venous thrombosis occurs in an unusual site such as mesenteric, hepatic or portal vein.
- Erythromelalgia: painful burning of hands accompanied by erythema (redness) that is relieved by aspirin.
- Qualitative defect in platelets leads to mucosal bleeding (platelets although large in number yet functionally useless).
- Splenomegaly is present in 25% of cases.

INVESTIGATIONS

Blood CP

- Very markedly high platelet count. WBC count is often mildly elevated.
- Hematocrit is normal. RBC morphology is normal.
- Peripheral film shows large sized platelets.

Bone marrow

Bone marrow shows increased number of megakaryocytes

DIFFRENTIAL DIAGNOSIS

Essential thrombosis should be differentiated from secondary causes of elevated platelet count (secondary thrombocytosis) as following:

- **Reactive thrombocytosis**: platelet count is high but usually not exceed 10,000,000/μL while in essential thrombocytosis it may be over 20,000,000/ μL.
- **Inflammatory disorders:** such as rheumatoid arthritis, ulcerative colitis.
- *Chronic infections.*
- *Iron deficiency.*
- *After splenectomy*

TREATMENT

- Hydroxyurea controls the platelet count to prevent the risk of thrombosis.
- Aspirin.
- Plateletpheresis in case of severe bleeding.

MYELODYSPLASTIC SYNDROME

Myelodysplastic syndromes (or myelodysplasia) are a group of acquired bone marrow disorders that are due to a defect in stem cells. Despite the presence of adequate numbers of hemopoietic stem cells ineffective hematopoiesis occurs and failure of bone marrow results in cytopenias. Myelodysplasia is usually idiopathic but may occur after chemotherapy for some malignant disorder. About 30% cases of myelodysplasia transform into acute myelogenous leukemia; therefore this is also called preleukemia.

TYPES

1. Refractory anemia.
2. Refractory anemia with ringed sideroblasts.
3. Refractory anemia with an excess of blasts (blasts 5-20%).
4. Refractory anemia with an excess of blasts in transformation (blasts 20-30%)
5. Chronic myeomonocytic leukemia.

CLINICAL FEATURES

- Age of presentation over 60 years.
- Asymptomatic: diagnosed on abnormal blood count.
- Features of bone marrow failure such anemia, infection or bleeding.
- On examination splenomegaly may be present with anemia, bleeding and signs of infections.

INVESTIGATION

Blood CP

Anemia, neutropenia, thrombocytopenia either alone or in combination.

Bone marrow

- Bone marrow is hypercelular despite pancytopenia.
- Evidence of dyserythropoiesis.
- Abnormal morphology of granulocyte precursors and megakaryocytes.
- Ring sideroblasts are also present.
- The number of blast cells in the bone marrow is increased.

MANAGEMENT

Blast cells < 5%

- Conservative management with transfusion, platelets replacement and antibiotics.
- Erthropoietin and other hemopoietic growth factors.

Blasts > 5%

- *Supportive therapy*.
- *Chemotherapy* as in acute myeloblastic leukemia may be given in patients under the age 60.
- *Bone marrow transplantation*
  Patients under age 60 with matched sibling donors can be treated with allogeneic bone marrow transplantation. Cure rates are 30-50%.

PROGNOSIS

Myelodysplasia is an ultimately fatal disease, infection or bleeding are common cause of death.

MULTIPLE MYELOMA

- Multiple myeloma is a malignant disorder of plasma cells OR
- Multiple myeloma is a clonal proliferation of neoplastic plasma cells in the bone marrow.

PATHOPHYSIOLOGY

- Normal plasma cells are derived from B-lymphocytes. These plasma cells manufacture immunoglobulins (antibodies).
- When plasma cell malignancy occurs, number of atypical immunoglobulins (called paraproteins) become raised. The bone marrow is heavily infiltrated with atypical (malignant) plasma cells. Progressive replacement of the bone marrow occurs by atypical plasma cells with reduction of normal cells, resulting in bone marrow failure manifesting as anemia, thrombocytopenia and leukopenia.
- Although a small number of malignant plasma cells are present in circulation, the majority is present in bone marrow.
- The malignant plasma cells produce osteoclast activating factor and other cytokines resulting in bone resorption and hypercalcemia.
- Marrow involvement causes only anemia or pancytopenia, while the osteoclastic bone lesions cause bone pain, osteoporosis, fractures and hypercalcemia.
- Excessive production of atypical immunoglobulins (myeloma paraproteins) causes reduction in normal immunoglobulins, resulting in impairment of immune function leading to repeated infections especially pneumonias.

Life threatening complications

- Renal impairment- may require dialysis
- Hypercalcemia
- Hyperviscosity syndrome

CLASSIFICATION OF MULTIPLE MYELOMA

Types of paraprotein	Relative frequency
IgG	55%
IgA	21%
Light chain only	22%
Others	2%

RELATIONSHIP BETWEEN PATHOLOGY AND CLINICAL FEATURES IN MULTIPLE MYELOMA		
Pathology	**Effect**	**Clinical features**
Marrow involvement with malignant plasma cells	1. Bone erosion due to stimulation of osteoclasts. 2. Pathological fractures 3. Hypercalcemia 4. Bone marrow failure	1. Pain 2. Severe local pain 3. Lethargy, thirst 4. Anemia, tiredness
Excess production of paraproteins and light chains	1. Renal damage 2. Increased blood viscosity 3. Amyloidosis	1. Uremia 2. Blurred vision, headache, vertigo, stupor, coma 3. Nephrotic syndrome
Reduction in number of normal plasma cells	Impaired immune function	Susceptibility to infection, particularly respiratory

CLINICAL FEATURES

- *Bone pain* particularly in the ribs or axial skeleton.
- *Bacterial infection* – particularly pneumonia due to defective immunity.
- *Symptoms of anemia:* due to bone marrow depression from infiltration, chronic disease, renal failure or treatment.
- *Bleeding tendency:* due to reduced platelet function.
- *Renal disease symptoms:* due to hypercalcemia, hyperuricemia, tubular damage by paraproteins, UTI or amyloidosis.
- *Features of hypercalcemia* e.g. thirst, polyurea.
- *Spinal cord compression* causing kyphoscoliosis.
- *Skin changes*: purpura, pruritus
- *Hyperviscosity syndrome* due to excessive paraprotein causing blurred vision, headache, vertigo, stupor, coma.

CLINICAL FEATURES OF MULTIPLE MYELOMA

- Weight loss, malaise and fatigue occur
- 60% present with bone pain, particularly back and rib pain.
- Anorexia, vomiting, diarrhoea or constipation and polyuria occur with hypercalcaemia, which is present in 30%
- Hypercalcaemia and dehydration contribute to renal impairment, which is present in 50% at diagnosis
- Pneumococcal, chest and urinary tract infections are common due to failure of production of normal immunoglobulins
- Headache, confusion, breathlessness: visual disturbance and bleeding can occur secondary to hyperviscosity, which is particularly associated with IgA proteins.
- Some 5% present with paralysis secondary to spinal cord compression by an extradural plasma cell mass.
- Carpal tunnel syndrome, nephritic syndrome, cardiac failure and neuropathy can occur secondary to amyloid deposition.

INVESTIGATIONS

Diagnosis of myeloma requires the detection of at least two of the following abnormalities:

1. Presence of paraprotein on serum protein electrophoresis – In serum of 80% and in urine (Bence Jones proteins) 20%.
2. Bone marrow biopsy shows infiltration of the marrow with malignant plasma cells ranging from 5-100%.
3. X-rays show osteolytic lesions, they are most commonly seen in the axial skeleton: skull, spine, proximal long bones and ribs.

Bone scan is not useful in detecting bone lesion in myeloma, as there is no osteoblastic component.

Other labs

- Hypercalcemia
- Renal failure
- Raised ESR
- Alkaline phosphatase is not elevated despite extensive bony involvement.
- Some patients have proximal renal tubular acidosis.
- Urinalysis may reveal proteinuria.

POINTS TO NOTE IN THE DIAGNOSIS OF MYELOMA

- In the absence of fractures or bone repair the plasma alkaline phosphatase and the bone scan are normal.
- Serum β2-microglobulin estimations may provide a useful assessment of prognosis.
- The absence of immune paresis (reduction of normal immunoglobulins below normal levels) should cast doubt on the diagnosis.
- Only about 5% of patients with an ESR persistently above 100 mm in the first hour have myeloma

MANAGEMENTS

1. Supportive
2. Specific

Supportive

- High fluid intake to treat renal impairment and hypercalcemia.
- Analgesics for bone pain.
- Biphosphonates for hypercalcemia; it also prevents pathological fractures.
- Allopurinol to prevent uric acid nephropathy.
- Plasma pharesis may be required for hyperviscosity.

Specific

Chemotherapy

In older patients melphan is an effective oral therapy while in young patients IV therapy with VAD (Vincristine, Adriamycin, Dexamethasone).

Radiotherapy:

Radiotherapy is useful for local problems such as bone pain, pathological fractures and tumorous lesions (called plasmacytomas).

Transplantation

Autologous stem cell transplantation may improve quality of life in patients less than 60 years.

Bisphosphonates

Chronic bisphosphonate therapy reduces bone pain and fractures.

Thalidomide

The drug has anti- angiogenic effect against blood vessels supplying tumors. It is given in refractory myeloma and combined with dexamethasone.

PROGNOSIS

Median survival in patients taking standard treatment is approximately 40 months.

Poor prognostic features at diagnosis in multiple myeloma

- A hemoglobin concentration of less than 7 mg/dl
- Severe hypoalbuminemia
- Intractable renal failure
- Thrombocytopenia
- High (β2-microglobulin levels
- Plasma cell leukemia

WALDENSTORM'S MACROGLOBINEMIA

This is a malignant disorder of B cells that appears to be a hybrid of lymphocytes and plasma cells (i.e. it is a low grade lymphoplasmacytoid lymphoma) that secretes IgM paraproteins. It is a monoclonal gammopathy in which there is over- production of IgM immunoglobulins (paraproteins).

Clinical features

Patients are in their 60s or 70s presenting with hyperviscosity syndrome or bone marrow failure (anemia) due to infiltration. On examination hepatosplenomegaly , lymphadenopathy and anemia may be present.

Investigations

- Anemia with increase in plasma volume due to presence of paraproteins.
- Abnormal plasmacytic lymphocytes usually appear in small number in peripheral film while the bone marrow is infiltrated by the plasmacytic lymphocytes.
- Serum protein electrophoresis: shows monoclonal IgM spike in the beta or gamma globulin region.
- Serum viscosity is increased.

Differential diagnosis

- Monoclonal gammopathy of unknown significance (in which there is no bone marrow infiltration).
- Multiple myeloma and chronic lymphocytic leukemia: Waldenstorm's macroglobulinemia is differentiated from these disorders by bone marrow morphology and characteristic IgM spike on plasma electrophoresis.

Treatment

- Hyperviscosity syndrome: urgent plasmapharesis.
- Intermittent therapy with chlorambucil and cyclophosphomide.
- Autologous stem cell transplantation.

BLEEDING DISORDERS

These disorders are characterized by spontaneous bleeding or excessive bleeding following trauma.

IMPORTANT POINTS FOR HISTORY OF BLEEDING DISORDERS

Site of bleeds
Muscle and joint bleeds indicate a coagulation defect, whereas purpura, prolonged bleeding from superficial cuts, epistaxis, gastrointestinal hemorrhage or menorrhagia indicate a failure of platelets or possibly the presence of von Willebrand disease. Recurrent bleeds at a single site suggest a local structural abnormality.

Duration of history
It may be possible to assess whether the patient has a congenital or acquired disorder by whether the patient has had a life-long propensity to bleeding or a short history suggestive of an acquired cause.

Precipitating causes
Bleeding that arises spontaneously indicates a more severe defect than if hemorrhage only arises after trauma.

Surgery
Enquiry about all operations is useful but particularly dental extractions, tonsillectomy and circumcision as these are all very stressful tests of the haemostatic system. Bleeding that starts immediately after surgery indicates defective platelet plug formation whereas that which comes on after several hours is more indicative of failure of platelet plug stabilization by fibrin due to a coagulation defect.

Family history
Absence of other relatives with clinically significant bleeding does not exclude a hereditary bleeding diathesis; about one-third of cases of hemophilia arise in individuals without a family history.

Systemic illnesses
Many diseases, or their treatment may occasionally be associated with bleeding but it is a particularly important to consider the possiblityof hepatic or renal failure, paraproteinaemia or a collagenosis.

Drugs
Almost any drug can potentially produce bleeding either by depressing marrow function with consequent thrombocytopenia or by interfacing with warfarin Nonsteroidal anti-inflammatory drugs inhibit platelet function; the effect of aspirin may last for up to 10 days after a single tablet

INFORMATION OBTAINED FROM INVESTIGATION FOR HEMOSTATIC FUNCTION

Blood film
- Evidence of underlying disease, e.g. leukaemia
- Platelets numbers & morphology
- RBC morphology,
- Microangiopathic haemolysis – RBC fragments.

Platelet count
Thrombocytopenia

Bleeding time
- Platelet dysfunction
- Thrombocytopenia
- Von Willebrand's disease

PT (extrinsic pathway)
- Warfarin therapy
- Liver disease
- Disseminated intravascular coagulation

APTT (intrinsic pathway)
- Heparin therapy
- Hemophilia A and B
- Disseminated intravascular coagulation

Fibrinogen concentration
- Congenital hypofibringenaemia
- Disseminated intravascular coagulation

D dimmers
- Fibrinolysis
- Disseminated intravascular dission

ETIOLOGY OF BLEEDING DISORDERS

1. *Vascular disorders (Increased fragility of the vessels)* Vessel wall abnormalities occur in severe vitamin C deficiency (scurvy), and in infectious and hypersensitivity vasculitis (e.g. in infective endocarditis).
2. *Platelet disorders (dysfunction or deficiency):* Platelet dysfunction is seen in uremia, after aspirin ingestion. Platelet deficiency is seen in bone marrow failure, SLE & drug induced thrombocytopenia.
3. *coagulation disorders (Derangement in the clotting mechanism).*

Vascular disorders

Abnormalities of vascular walls such as vasculitis may result in a propensity to purpuric lesions (bleeding in skin), which are often slightly elevated. The vascular disorders include the following:

Hereditary hemorrhagic telengiectasia

It is an autosomal dominant disorder causing dilatation of capillaries and small arterioles producing characteristic small red spots (purpura) that blench on pressure in skin and mucus membrane particularly nose, GIT, lung, fingertips, face and tongue. Recurrent epistaxis and chronic GI bleeding are the major problems and may cause iron deficiency anemia. A significant number of these patients develop larger pulmonary AV malformations that cause hypoxemia due to right-to- left shunt and predisposing individuals to paradoxical embolism.

Local cautery or laser therapy may be effective to prevent bleeding from single lesions, while treatment of bleeding from multiple lesions is difficult; just give iron therapy to prevent anemia.

Other vascular disorders are:

- Scurvy (due to vitamin C deficiency)
- Easy bruising syndrome
- Senile purpura
- Purpura due to infection such as meningococcal infection, septicemia, measles, typhoid.
- Purpura due to allergic disorders such as Henoch- Schonlein purpura, SLE, RA.
- Purpura due to connective tissue disorders such as Ehler-Danlos syndrome, Marfan's syndrome.
- Drug induced purpura with steroids, sulphonamides.

Platelet disorders

Platelet disorder lcausing bleeding may be due to impaired platelet function (qualitative defect) or decrease in number of platelets.

CAUSES OF QUALITATIVE PLATELET DYSFUNCTION

CONGENITAL
- Storage pool disease
- Bernaurd-Soulier syndrome

ACQUIRED
- Drugs: aspirin and other NSAIDS, penicillins, cephalosporins, heparin, betablockers.
- Myeloproliferative disease
- Uremia
- Autoantibody
- Paraproteins
- Fibrin degradation products
- Acquired storage pool disease

VON WILLEBRAND'S DISEASE

THROMBOCYTOPENIA

Reduced platelet count is called thrombocytopenia. It may arise by one of the three mechanisms.

1. Failure of megakaryocyte maturation
2. Excessive platelet consumption after their release into the circulation (e.g. in DIC and ITP).
3. Platelet sequestration in the enlarged spleen (e.g. in hypersplenism).

CAUSES OF THROMBOCYTOPENIA

Impaired production due to bone marrow failure
- Megaloblastic anemia
- Infiltration
- Leukemia
- Multiple myeloma
- Solid tumor infiltration
- Myelofibrosis
- Aplastic anemia due to drugs, chemicals, viruses and paroxysmal nocturnal hemoglobinuria.

Excessive destruction
- Disseminated intravascular coagulation (DIC)
- Idiopathic (autoimmune) thrombocytopenic purpura
- Immunological destruction in SLE, CLL, heparin, viruses (HIV, Epstein- Barr virus)
- Thrombotic thrombocytopenic purpura
- Hemolytic uremic syndrome

Platelet sequestration (due to hypersplenism as in cirrhosis and lymphomas).

IDIOPATHIC (AUTOIMMUNE) THROMBOCYTOPENIC PURPURA (ITP)

In idiopathic thrombocytopenic purpura autoantibodies are present against platelet membrane, causing premature removal of platelets from circulation by the monocyte-macrophage system (the antibody- coated platelets are removed by macrophages).

CLINICAL FEATURES

Acute ITP

Acute ITP is usually seen in children often presents 2-3 weeks after viral infection with sudden onset of purpura and some times oral and nasal bleeding. Peripheral blood film shows reduced platelet count while the bone marrow reveals increase in megakaryocytes.

Chronic ITP

Chronic ITP is characteristically seen in adult women. Peak incidence at age 20-50 years. Patients are syste..iically well, not febrile, presenting complaint is epistaxis, oral bleeding, menorrhagia, purpura or petechiae.

ITP is usually idiopathic but may occur in association with other autoimmune disorders such as SLE, thyroid disease and autoimmune hemolytic anemia, CLL anf after infections with viruses such as HIV.

On examination there is no splenomegaly, if present diagnosis of ITP is doubtful.

INVESTIGATIONS

- The hallmark of ITP is throbocytopenia. Other cell lines are normal. Platelets are slighty enlarged.
- *Bone marrow* shows normal or increased number of megakaryocytes.
- *Detection of platelet autoantibodies* is not essential for confirmation of diagnosis. Diagnosis depend on exclusion of all other causes of excessive destruction of platelets.

TREATMENT

Acute ITP in children usually remits spontaneously. Treatment in acute phase with steroids or high dose immunoglobulin is required only when platelet count is less than 20,000/µL. and there is bleeding.

In chronic ITP spontaneous remission is rare and they need therapy.

Prednisolone (Deltacortil)

Prednisolone 1-2 mg/kg/day is given to adults. It decreases affinity of splenic macrophages for antibody – coated platelets. Platelet count usually begins to rise within a week and response is almost always in 3 weeks. High dose therapy should be continued until platelet count is normal then gradually reduce the dose to the minimum effective dose (usually 5mg/day), complete withdrawal of prednisolone causes recurrence of thrombocytopenia.

The risk of bleeding is small with platelet count more than 50,000/µL.

Transfused platelets survive no longer than the patient's own platelets but may be beneficial in life-threatening bleeding.

Platelet transfusion is required when:

- Platelet count is less than 10,000/µL.
- Troublesome bleeding such as persistent epistaxis.
- Life – threatening bleeding such as GI hemorrhage.

Splenectomy

It is the most definitive treatment for ITP Splenectomy is indicated if patients do not respond to prednisolone initially or require very high doses to maintain adequate platelet count. Splenectomy can be performed safely even on platelet count less than 10,000/µL.

Immunoglobulins

High dose immunoglobulin 1g/kg/d for 1-2 days is highly effective in rapidly rising platelet count by blocking Fc receptors on macrophages in the spleen. The response rate is 90% and platelet cour increases within 1-5 days. However this effect last for 2-weeks only. Therefore immunoglobuli therapy is reserved for bleeding emergencies, an for preparing patient for splenectomy.

Danazol

Patients not responding to prednisolone and splenectomy may be given danazol 600mg/d with response rate in 50% of cases.

Immunosuppressive therapy

In refractory cases immunosuppressive drugs such as vincristine, vinblastine, azathioprine cyclosporine, and cyclophosphomide.

PROGNOSIS

In most patients prednisolone controls initially and then splenectomy provides definite treatment. Intracerebral hemorrhage may occur when platelet count is < 5000/μL.

THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP)

TTP is a rare but very serious condition in which platelet destruction leads to profound thrombocytopenia. There is damage to endothelial cells of the microcirculation which is followed by platelet adherence and fibrin deposition causing thrpmbosis in microcirculation (arterioles). When the RBCs pass through these arterioles they are destroyed resulting in intravascular hemolysis. Therefore it is a syndrome of microangiopathic hemolytic anemia, thrombocytopenia and markedly elevated serum LDH (due to intravascular hemolysis). Pathologically thrombi may be seen in arterioles and capillaries of various organs causing their dysfunction.

Fever, neurologic disorders and renal failure are presenting features along with hemolytic anemia and thrombocytopenia. Cause is unknown, however there is some association with E.coli infection, pregnancy, HIV, SLE, scleroderma and Sjogren's syndrome.

Clinical features

- TTP is seen primarily in young aged 20-50 years, slightly more common in females.
- Patient presents with anemia (due to hemolysis), bleeding (due to thrombocytopenia) and fever. Neurological features may be present such as headache, confusion, aphasia, seizure, hemiparesis and coma.
- Renal involvement causes renal failure

Investigations

- Investigations show anemia, reticulocytosis, and occasionally circulating nucleated red cells.
- The hallmark is microangiopathic blood picture with fragmented red blood cells.
- Thrombocytopenia is present; WBC count may be raised.
- Hemolysis is indicated with increased indirect bilirubin. LDH is markedly elevated.
- Coagulation screen such as PT, APTT, fibrinogen and fibrin degradation product (FDP) are usually normal.

Management

- Plasma pharesis (plasma exchange) daily until patient is in complete remission. About 60-80 ml/kg of plasma is removed and replaced with fresh frozen plasma (FFP)
- Prednisolone and antiplatelet (aspirin) are also used in addition to plasmapharesis.
- Combination of splenectomy, corticosteroids and dextran in resistant cases. Immunosuppressive therapy with cyclophosphomide may be effective if patient do not respond to plasma pharesis.

Coagulation disorders

In previous we have discussed two causes of bleeding disorders; vascular disorders and platelet disorders, now we will discuss the last one i.e. coagulation disorders.

Inherited coagulation disorders

Hemophilia A, hemophilia B, Von Willebrand's disease.

Acquired coagulation disorders

Vitamin K deficiency, liver disease and DIC

HEMOPHILIA

It is a hereditary disease mainly affecting males but transmitted by females and characterized by prolonged coagulation and a life-long tendency to excessive hemorrhage. There are two types:

1. Hemophilia A (true hemophilia): when antihemophilic factor (Factor VIII: C) is deficient
2. Hemophilia B when Christmas factor (IX) is deficient.

HEMOPHILIA A

Clinical features

Although it is a congenital disorder bleeding occurs as bruising when babies are about 6 months old when they begin to move about, trauma results in excessive bleeding.

Individual with severe hemophilia present with recurrent hemorrhage of the following site.

- Joints: most characteristic site, knees, elbows, ankles & hips are commonly affected. Joints become hot, swollen & very painful.
- Mucous membrane & internal bleeding of mouth gums, lips, brain, kidney.
- Muscle hematoma: especially of calf & psoas muscles.

SEVERITY OF HEMOPHILIA

Severity	Factor VIII or IX level	Clinical presentation
Severe	<2%	Spontaneous hemarthosis and muscle hematoma
Moderate	2-10%	Mild trauma or surgery causes hematomas
Mild	10-50%	Major injury or surgery results in excess bleeding.

Investigations

- Bleeding time (BT): normal
- PT: normal
- APTT: raised.
- Factor VIII:C is low.
- vWF: normal

Management

- Factor VIII concentrate by IV infusion.
- Recombinant factor VIII.
- Synthetic vasopressin rises factor VIII: C in mild cases.

HEMOPHILIA B (Christmas disease)

Clinical features

Similar to hemophilia A

Management

Inj. Factor IX I/V infusion

LONG-TERM SEQUELAE OF HAEMOPHILIA

Complications due to repeated hemorrhages

1. Arthropathy of large joints, e.g. knees, elbows
2. Atrophy of muscles secondary to hematomas
3. Mononeuropathy resulting from pressure by hematomas

Complications due to therapy

1. Anti-factor VIII antibody development
2. Virus transmission
   Hepatitis A, B, C, D viruses
   Human immunodeficiency virus – AIDS

VON WILLEBRAND'S DISEASE

Von Willebrand's disease is the most commoi congenital disorder of hemostasis. It is transmitte‹ in an autosomal dominant pattern. It i: characterized by deficient or defective von Willebrand factor. Von Wilibrand's factor plays a role in platelet adhesion to damaged subendothelium as well as stabilizing factor VIII:C in plasma, therefore its deficiency or abnormality causes defective platelet function as well as factor VIII:C deficiency.

Clinical features

- Von Willebrand's disease is a common disorder affecting both men and women.
- Most bleeding is mucosal (epistaxis, gingival bleeding, menorrhagia and GI bleeding.
- Bleeding follows minor trauma or surgery.
- Aspirin increases bleeding while pregnancy and estrogen use decreases bleeding.

Investigations

- Bleeding time (BT): increased
- PT: normal
- APTT: raised.
- Factor VIII:C is low.
- vWF: low

In Von Willibrand disease bleeding time i: prolongs while in hemophilia A bleeding time i: normal.

Treatment

- *Mild hemorrhage:* synthetic vasopressin which raises the Von Willebrand factor.
- *Massive hemorrhage:* factor VIII concentrates that contain considerable quantities of Von Willebrand factor in addition to factor VIII.

DISSEMINATED INTRAVASCULAR COAGULATION (DIC)

Disseminated intravascular coagulation is a condition characterized by thrombosis within the circulation: As a consequence of widespread thrombosis, there is consumption of platelets and coagulation factors with secondarily activation of fibrinolysis, leading to bleeding tendency. Most of the DIC patients admitted in our ward were shifted from Gyne/obst department with septicemia due to septic abortion or retained dead fetus and with retained products of conception (RPOCs).

CAUSES OF DIC

Infections

- Gram negative bacilli
- Neisseria meningitides
- Streptococcus pneumoniae
- Falciparum malaria

Cancers

- Lung
- Pancreas
- Prostate

Obstetrics

- Abruptio placentae
- Retained dead fetus
- Pre-eclampsia
- Amniotic fluid embolism

Others

- Hemolytic transfusion reaction
- Trauma, burn, surgery
- Liver disease
- Snake bite

CLINICAL FEATURES

DIC leads to both bleeding and thrombosis; bleeding is far more common than thrombosis.

- **Bleeding:** bleeding may occur at any site but spontaneous bleeding and oozing at venepuncture sites are clue to diagnosis. Bleeding in skin causes purpura and echymosis. Mouth, nose, GIT hemorrhage may occur.
- **Thrombosis:** occurs due to vessel occlusion by fibrin and platelets. Skin, brain and kidneys are mostly affected, causing digital ischemia and gangrene, renal cortical necrosis, hemorrhagic adrenal infarction.
- Microangiopathic hemolytic anemia.
- Other manifestations: High incidence of cardio respiratory, renal failure & jaundice.

Subacute DIC is seen primarily in cancer patients and manifests as recurrent superficial and deep venous thrombosis (Trousseau's syndrome).

INVESTIGATION

Characteristic findings of DIC on investigations are:

- Thrombocytopenia
- Prolongation of PT.
- APTT may or may not be prolonged
- Low fibrinogen
- Increased levels of fibrin degradation products (FDP) in which D-dimer is the most sensitive fibrin degradation product indicating fibrinolysis.
- Microangiopathic hemolytic anemia in 25% with fragmented RBCs on peripheral blood film.
- Antithrombin III level: may be very low.
- In subacute DIC there is only thrombocytopenia and elevated D-dimer; fibrinogen and APTT may be normal.

TREATMENT

Treatment of underlying cause

General measure:

Correction of dehydration, renal failure & acidosis and treatment of shock.

Replacement therapy

- Platelet count should be maintained above 50,000/μL with platelet transfusion.
- Fibrinogen is replaced with cryoprecipitates to maintain plasma fibrinogen above 150mg/dl. One unit of cryoprecipitates elevates 6-8 mg/dl.
- Coagulation factor deficiency can be corrected with fresh frozen plasma (FFP). Usually 7-14 units are required.
- When there is deep venous thrombosis, pulmonary embolism or peripheral gangrene then give anticoagulant (Heparin).

SOME. IMPORTANT TERMS AND THEIR MEANINGS

Microcytosis
This average size of the red cells is reduced. The mean cell volume is reduced. It is commonly found in iron deficiency anemia and other disorders of hemoglobin synthesis (e.g. thalassemias)

Macrocytosis
The average size of red cells is greater than normal. The mean cell volume is increased. It is seen, for instance, in megaloblastic anemia but its occurrence does not necessarily mean a megaloblastic change in the marrow. A common cause is excessive alcohol consumption.

Hypochromia
The red cells contain less than the normal amount of hemoglobin and they stain less deeply. They show greater than normal central pallor. Hypochromia is commonly associated with microcytosis and is a characteristic feature of disorders of hemoglobin synthesis, most commonly iron deficiency.

Anisocytosis
Inequality in the size of the red cells. It is found in many forms of anemia but is very prominent in megaloblastic anemia

Polkliocytosis
Marked irregularity in the shape of the red cells. It is never present without anisocytosis and usually reflects dyserythropoesis

Target cells
Abnormally flat red cells with a central mass of hemoglobin surrounded by a ring of pallor and an outer ring of hemoglobin. They are commonly associated with liver disease, impaired or absent splenic function (hyposplenism) and hemoglobinopathies.

Polychromasia – and reticulocytosis
Young red cells when stained by the Romanowsky method have a faint bluish color (basophilia) due to residual ribosomal material. A blood film in which such cells are present in increased numbers along with those of normal orange color is said to show polychromasia. This, like reticulocytosis, indicates increased production of new red cells by the bone marrow.

Punctate basophilia (basophilic stippling)
Abnormally damaged young red cells may show scattered deep-blue dots in the cytoplasm with Romanowsky staining. Such punctate basophilia may be found in any severe anemia but the presence of many of these cells is most commonly seen in beta-thalassaemia and chronic lead poisoning, where it may occur when the anemia is slight.

Howell-Jolly bodies
Remnants of nuclear material left in the erythrocyte after the nucleus is extruded. They are normally removed by the spleen and their presence usually indicates a non-functioning or absent spleen. Their numbers are greatly increased in certain erythropoietic disorders, e.g. megaloblastic anemia.

Nucleated red cells
Usually normoblasts found in the blood when erythropoiesis is very vigorous or when there is irritation of the bone marrow, as in leukemia or infiltration by secondary tumor.

Hypersegemented polymorphs
Present when the polymorphs have five or more lobes or there are any with six lobes. B12 and folic acid deficiency are common causes.

Leuco-erythroblastic picture
A blood picture in which primitive granulocytes and erythroblasts are simultaneously present in the peripheral blood. It is usually, but not necessarily, associated with anemia and reflects bone marrow irritation, as in malignant infiltration of the marrow, or disordered hemopoiesis, as in myelofibrosis. It can occur as a reaction to severe hemolysis or bleeding.

NEUROLOGICAL DISEASES 9

EXAMINATION OF NERVOUS SYSTEM

Examination of CNS comprises conscious level, higher mental function, motor system, sensory system and cranial nerves. Examiner's command may be to perform any one component (usually) or the whole system (rarely). Motor system and cranial nerve examination are very frequently asked in viva.

1. **Conscious level**

2. **Higher mental function**
   - Cognitive skills
   - Memory
   - Reasoning
   - Emotional status

3. **Motor system**
   - Bulk
   - Tone
   - Power
   - Reflexes
   - Coordination (cerebellum)
   - Gait (on lower limb examination)

4. **Sensory system**
   - Touch
   - Pain
   - Temperature
   - Vibration
   - Position
   - Stereognosis
   - Cortical sensation

5. **Cranial nerves**

6. **Examination of unconscious patient**

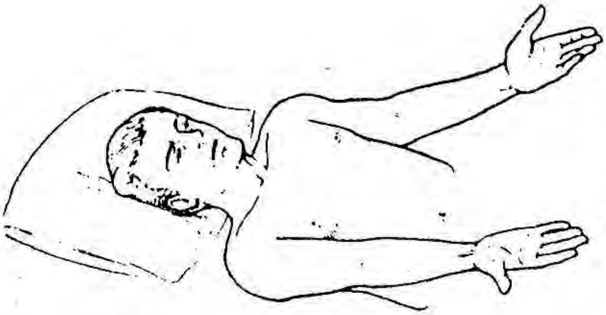
CONSCIOUS LEVEL

Conscious level of the patient is assessed by the Glasgow coma scale (GCS) based on assessment of eye opening, verbal response and motor response. GCS has maximum score 15 and minimum 3. Always mention conscious level in term of GCS.

GLASGOW COMA SCALE

Eye opening (E)	
• Spontaneous	4
• To speech	3
• To pain	2
• Nil	1
Motor response (M)	
• Obeys commands such as open the mouth	6
• Localizing to pain apply painful stimulus supranorbital nerve, patient brings hand up beyond the chin to localize.	5
• Withdraws	4
• Abnormal flexion (decorticate posture). On painful stimulus patient's elbows are flexed.	3
• Extensor response (decerebrate posture). In response to painful stimulus elbow extension occurs accompanied by spastic flexion of the wrist.	2
• Nil	1
Verbal response (V)	
• Oriented: in time, place, person	5
• Confused conversation: talking in sentences but disoriented in time, place and person.	4
• Inappropriate words: utters words rather than sentences .	3
• Incomprehensible sounds: groans or grunts, but no words.	2
• Nil.	1

Coma score= E+M+V (minimum =3, maximum = 15)



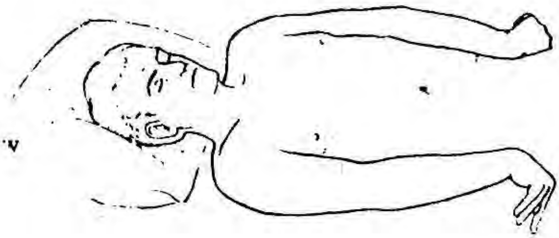
Obeys commands



Localizing to pain



Flexion to pain (Decorticate posture)



Extension to pain (Decerebrate posture)

HIGHER MENTAL FUNCTIONS

Cognitive skill

Features of normal cognition are:

- Fluent language
- Understanding of spoken commands
- Naming the objects
- Reading and writing
- Numerical calculation
- Recognition of objects
- Ability to find the way
- Ability to dressing himself
- Ability to copy a geometric patterns such as cube, star, circle.

Memory

- *Recent memory*: ask about present illness, any hot news.
- *Remote memory*: ask about the events occurring more than 5 years.

Reasoning and problem solving

Ask the patient to reverse 3 or 4 random numbers or to explain proverbs.

Emotional state

Examine for depression, anxiety, excitement, and slowness of movement.

MOTOR SYSTEM

In motor system we examine appearnce, tone, power, reflexes and coordination as following:

APPEARANCE

- Asymmetry or deformity
- Muscle wasting
- Muscle hypertrophy
- Muscle fasciculations: irregular non-rhythmical contraction of groups of motor units, increased after exercise and on tapping muscle surface.

TONE

Tone is assessed by alternate flexing and extending the large joints. Feel for hypertonia or hypotonia in the following way:

1. *Passive movements* of the elbow and wrist joints in upper limb and knee and ankle joints in lower limb.
2. *Holding the arms in front:* Ask the patient to hold arm outstretched, a sharp tap causes the

hypotonic arm to swing downward. In hypertonia there will be rebound effect and arms move upwards.

3. *Shaking wrist or ankle joints* results in increased range of movement in case of hypotonia.

Types of hypertonia (rigidity)

- *Clasp-knife rigidity*
  The initial resistance to movement is suddenly over come (seen in upper motor neutron lesion such as stroke and multiple sclerosis).
- *Lead-pipe rigidity*
  A steady increase in resistance throughout the movement (due to extrapyramidal lesion of basal ganglia) seen in extrapyramidal syndrome (EPS) and neuroleptic malignant syndrome (NMS).
- *Cog-wheel rigidity*
  Ratchet – like increase in resistance giving it a jerky feel (due to Parkinsonism)

Hypotonia

Hypotonia is the feature of lower motor neuron lesion, cerebellar disorders and early phase of stroke before spasticity develops.

Clonus

Clonus is the term applied to a rhythmic series of involuntary muscle contractions evoked by sudden stretch of the muscle. It is a feature of upper motor neuron lesion. Clonus can be evoked on ankle and knee as following:

<u>*Ankle clonus*</u>

Support the flexed knee with one hand in the popliteal fossa so that the ankle rests gently on the bed. Using the other hand and briskly dorsiflex the foot and sustain the pressure, there will be a rhythmical beating (alternate plantar flexion and dorsiflexion) of the foot for as long as the pressure is maintained.

<u>*Knee clonus*</u>

Sharply push the patella towards the foot while the patient lies supine and relaxed and the knee extended. Following the initial jerk, exert sustained pressure with the thumb and index finger in a downward direction on the patella, the patella will jerk up and down.

Testing for ankle clonus

POWER

Muscle strength is assessed by gauging the examiner's ability to overcome the patient's full voluntary muscle resistance.

Examine muscle power in individual muscle group in both limbs alternatively or simultaneously, so that strength of the right and left can be directly compared. Power is graded according to the following scheme and should be mentioned in term of grading:

GRADING OF POWER

0. No muscle contraction visible, complete paralysis.
1. Muscle contraction visible, but no movement of joint.
2. Movement is possible when gravity is excluded i.e. patient can move limb horizontally on bed but unable to elevate.
3. Movement possible against gravity but not against resistance i.e. when patient is asked to elevate the limb he is able to elevate, however not able to move the limb if further resistance is added.
4. Movement is possible against gravity and some resistance.
5. Normal power.

If power is reduced decide whether:

- This is symmetrical or asymmetrical
- Proximal, distal or general
- Painful joint or muscle disease interfering with the assessment.

UPPER LIMBS

Drift test
Ask the patient to hold arm outstretched with hands supinated for up to one minute. The eyes are closed (otherwise visual compensation occurs). The weak arm gradually pronates and drifts downwards.

Fingers
Flexors of fingers
Ask the patient to squeeze two fingers as tightly as possible and pull your fingers.

Extensors of fingers
Ask the patient to open the fist against resistance.

Adductors of fingers
Palmar interossei are adductors of fingers. They are tested by asking the patient to hold paper in between the fingers and try to remove it.

Abductors of fingers
Dorsal interossei are abductors of fingers. They are tested by asking the patient to fan out the fingers against resistance.

Wrist
Flexors of wrist
Ask the patient to bend the elbow and pull so as not to let the examiner straighten it out.

Extensors of wrist
Ask the patient to extend the wrist and not allow the examiner to bend it.

Elbow
Flexors of elbow
The patient should bend the elbow and pull so as not to let the examiner straighten it out.

Extensor of elbow
Patient is asked to straighten the flexed elbow against resistance.

Shoulder
Abductors of shoulder
The patient is asked to abduct the arms with the elbow flexed and resist the examiner's attempt to push them down.

Abductors of shoulders
The patient is asked to adduct the arms with the elbow flexed and not allow the examiner to separate them.

Flexion and extension of shoulder against resistance.

LOWER LIMBS

Hip
Hip flexors
Ask the patient to lift up the straight leg against resistance with the knee extended.

Hip extensors
Force the elevated leg down towards the bed against resistance.

Hip abductors
Ask the patient to abduct the leg and not let the examiner to push it in.

Hip adductors
Ask the patient to keep the leg adducted and not let you push it out.

Knee
Knee flexors
Ask the patient to bend the knee and not let you straighten it.

Knee extensors
With the knee slightly bent, ask the patient to straighten the knee against resistance.

Ankle
Plantar flexors
Ask the patient to push the foot down and not let you push it up.

Dorsiflexors
Ask the patient to bring the foot up and not let you push it down.

Evertors
With the foot in plantar flexion, ask the patient to evert the foot against resistance.

Invertors
Ask the patient to evert the foot against the resistance.

REFLEXES

- Patient should be in a comfortable and relaxed position.
- Ensure that the muscle being tested is visible.
- Strike the tendon, not the muscle belly.
- Observe the muscle contraction.
- **Reinforcement**: When reflexes are difficult to elicit, use technique of reinforcement e.g. for lower limb reflexes ask the patient to interlock the flexed fingers and tighten immediately before striking the tendon. For upper limb reflexes, ask the patient to clench the teeth. Do not declare diminished or absent reflexes until you have performed reinforcement procedures.

Deep tendon reflexes

- Biceps reflex (C5, C6)
- Triceps reflex (C7, C8).
- Brachioradialis reflex (C5, C6)
- Knee reflex (L3, L4)
- Ankle reflex (S1, S2)
- *Hoffinann reflex:* place the examining right index finger under the distal interphalangeal joint of the patient's middle finger, briskly flick down the patient's fingertip with the examining right thumb tip, observe the movement of patient's thumb. Reflex flexion of thumb is exaggerated in hyper- reflexia.

Grading of reflexes

0 ---- indicates absent reflexes
+ ---- reduced reflexes
++ ---- normal reflexes
+++ ---- exaggerated reflexes
++++ ---- exaggerated reflexes and clonus

Causes of hyperreflexia

- Upper motor neuron lesion
- Anxiety

Causes of diminished or absent reflexes

- Lower motor neuron lesion
  - lesion of motor nerve (neuropathy)
  - lesion of anterior spinal cord root (e.g. due to spondylosis),
  - lesion of the anterior horn cell (e.g. in poliomyelitis).
  - Sensory root or sensory nerve
- Cerebellar lesion
- Myopathy

Superficial reflexes

Plantar reflex (S1, S2)
Abdominal reflexes (T7-T11)
Cremasteric reflex (L1)

Plantar reflex

After telling the patient about what is to occur, use a blunt object such as key to stroke up the lateral aspect of the sole, and curve inward before it reaches the toes. The normal response is the flexion of the big toe at metatarsophalangeal joint. The extensor response (Babinski's sign) is abnormal and is characterized by extension of the big toe (up going toe) and fanning of the other toes. This indicates upper motor neuron (pyramidal) lesion. Bilateral up going planters may be found after a generalized seizure or in patient with coma.

Superficial abdominal reflex

Stroke the upper and lower quadrants of the abdominal wall on each side rapidly but lightly with an orange stick and observe muscle contraction that causes movement of umbilicus. This reflex is lost in upper motor neuron lesion.

Cremastric reflex

Stroke the skin of upper thigh using an orange stick and observe the response of the ipsilateral testicle. This reflex is lost in upper motor neuron lesion or damage to L1, 2 spinal segments.

COORDINATION

Following tests are performed to test coordination (cerebellar lesion):

Finger nose test

Ask the patient to touch his or her nose with the index finger and then turn the finger around and touch the examiner's outstretched forefinger at nearly full extension of the shoulder and elbow. Look for the signs that indicate cerebellar lesion such as:

- Intention tremor – tremor increasing as the target is approached.
- Past pointing – patient's finger overshoots the target.

Rapidly alternating movements

Ask the patient to pronate and supinate his or her hand on the dorsum of other hand as rapidly as

possible. This movement is slow in cerebellar lesion, extrapyramidal disorder (e.g. Parkinsonism) and pyramidal disorders (e.g. internal capsule infarction).

Rebound

Ask the patient to lift the arms rapidly from the sides and then stop. Hypotonia due to cerebellar disease causes delay in stopping the arms.

Heel-shin test

Ask the patient to run the heel of one foot up and down the opposite shin at a moderate pace and as accurately as possible. N cerebellar lesion the heel wobbles all over the place with oscillations from side to side and over shooting.

SENSORY SYSTEM

Pain

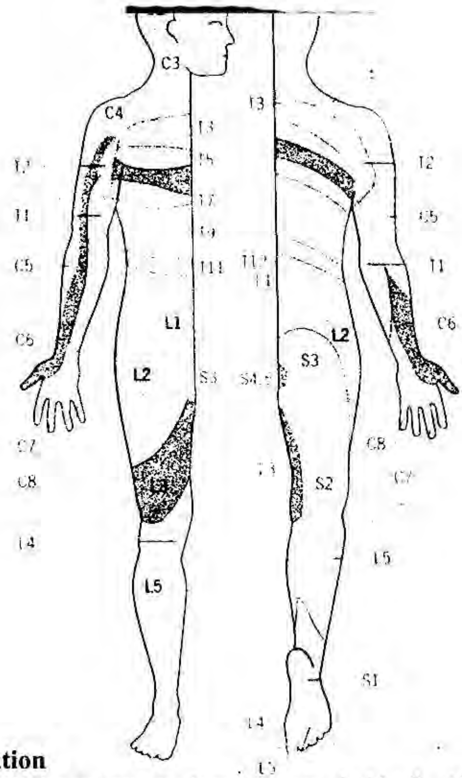
- Using a new pin, demonstrate to the patient that this induces a relatively sharp sensation by touching lightly a normal area such as anterior chest wall.
- Then ask the patient to close eyes and report if the quality of sensation changes, either blunter or sharper. Test each dermatome in limbs and over the trunk. Compare right with left in the same dermatome.
- Map out the extent of any area of dullness by going from area of dullness to the area of normal sensation.
- Sensation of touch, pain and temperature are impaired in peripheral neuropathies, nerve injuries and spinal injuries.

Touch

- Ask the patient to close the eyes and to respond verbally to each touch.
- Touch the skin with a small piece of cotton wool.
- Examine according to the area of spinal segment and compare with other limb and map out the area of abnormal sensation.

Temperature

This can be done in similar fashion like pain sensation, using tubes filled with hot and cold water. It is not routinely performed except in syringom.. lia.



Vibration

- Ask the patient to close the eyes, hold vibrating tuning fork over the sternum so that the patien identifies the sensation and describe feeling o vibration.
- In the lower limbs test the big toe, then ankle, tibial shaft and anterior iliac crest.
- In upper limbs test the interphalangeal joint of forefingers, then metacarophalangeal joints.
- The examiner then stops the tuning fork with the hand, and patient describes when this occurred. Compare on e side with other.
- Vibrating sense is lost earlier in diabetic neuropathy.

Proprioception (joint position sense)

- In upper limb use distal interphalangeal joint of index finger. When the patient has his eyes open, grasp the proximal phalanx of the finger with one hand while holding the medial and lateral borders of the distal phalanx with other thumb and finger and move it up and down to demonstrate these positions to the patient. Then ask the patient to close the eyes and repeat the same maneuver and ask the position of the distal phalanx. Test the other limb also.

- In the lower limb test the interphalangeal joint of big toe, holding the proximal phalanx in other hand.
- Proprioception sense is impaired in peripheral neuropathies, and in myelopathies affecting dorsal column.

Two-point discrimination

- Use an opened-out paper clip.
- Ask the patient to close the eyes, touch the two tips of clip to the finger pulp and ask the patient to determine if one or two stimuli were applied. Then determine the minimum distance at which two points are felt separately. In the normal person two separate stimuli can be discriminated when they are applied as close together as 3-5 mm on the pulp of index finger.
- Two-point discrimination in the finger is impaired in many peripheral neuropathies.

CRANIAL NERVES

No	Nerve	Function
I	Olfactory	Smell
II	Optic	Vision, fields, afferent light reflex
III	Oculomotor	Eyelid elevation, eye elevation, Adduction, depression in Abduction, efferent – to pupil
IV	Trochlear	Eye intorsion, depression in Aduction
V	Trigeminal	Facial and corneal sensation, muscles of mastication
VI	Abducent	Eye Abduction
VII	Facial	Facial movement, taste fibers
VIII	Vestibular Cochlear	Balance Hearing
IX	Glossopharyngeal	Sensation – soft palate, taste fibers
X	Vagus	Palatal movement, vocal cords, cough
XI	Accessory	Head turning shoulder shrugging
XII	Hypoglossal	Tongue movement

RAPID EXAMINATION OF CRANIAL NERVES

Practice to examine all cranial nerves quickly within 5 minutes (just remember the steps)

I: Olfactory nerve

- Each nostril is separately examined using non-pungent substances in bottles.

II: Optic nerve

1. *Visual acuity:* near vision is checked by reading book and far vision with the help of Snellen chart.
2. *Color vision* is checked with the use of Ishihara charts.
3. *Field of vision* is tested by the confrontation method.
4. *Fundoscopy*

III, IV, VI: Oculomotor, trochlear and abducent

1. *Eye lids*: ptosis
2. *Pupil:* shape, size, reaction to light, direct and indirect consensual light reflex, accommodation reflex.
3. *Eye movements* in all directions by asking the patient to follow the moving finger.

V: Trigeminal nerve

Sensory

Corneal and conjunctival reflexes by touching with cotton wisp.

Motor

- *Masseter:* clenching the teeth
- *Pterygoids:* ask the patient to open the jaw against resistance, and move the jaw laterally against resistance.

Jaw jerk: increased in upper motor neuron palsy of trigeminal nerve.

VII: Facial nerve

1. Ask the patient to look up and examine the wrinkles of forehead.
2. Ask the patient to close eyes tightly and you compare the two sides.
3. Look for nasolabial folds
4. Ask the patient to inflate the cheeks, show the teeth, and whistle.

VIII: Vestibulocochlear nerve

- Whisper in each ear to check deafness
- Perform Rinne's and Weber's tests

IX, X: Glossopharyngeal and vagus

1. Gag reflex: touch posterior pharyngeal wall, there will be contraction and elevation of pharyngeal wall on that side.

2. Palatal reflex: when soft palate is touched it moves upwards.

3. Ah test: Ask the patient to say "ah" and lok the symmetrical movement of soft palate.

4. Ask the patient to speak to assess hoarseness, to cough and swallow.

XII: Hypoglossal nerve

- Inspect tongue for wasting
- Ask the patient to protrude tongue, it deviates to the weaker side.

XI: Accessory nerve

- Ask the patient to shrungthe shoulder and feel trapezius while pushing the shoulder down.
- Ask the patient to turn the head against resistance and feel the bulk of sternocledomastoid.

NEUROLOGICAL INVESTIGATIONS

X-RAY SKULL may show:

- Fracture of skull vault or base
- Enlargement or destruction of pituitary fossa due to tumor or raised intracranial pressure.
- Intracranial calcification due to tuberculoma

X-RAY SPINAL CORD may show:

- Fractures
- Spondylosis (degenerative bone disease)
- Destructive bone lesion due to infection or metastasis.

COMPUTED TOMOGRAPHY (CT SCAN)

It is an x-ray slice of 5-10mm thickness in which different tissues have different densities.

Hypodense tissues (looking blackish)

Infarction tumor, abscess (having white rim and black center), cerebral edema, encephalitis and resolving hematoma.

CSF and air look blacker.

Hyperdense tissues (looking whitish)

Bone, blood (hemorrhage) and calcification

ADVANTAGES OF CT SCAN

CT scanning demonstrates.

- Cerebral tumors
- Intracerebral hemorrhage and infarction
- Subdural and extradural hematoma
- Subarachnoid hemorrhage
- Lateral shift of midline structures
- Cerebral atrophy
- Pituitary mass lesion.

LIMITATIONS OF CT SCAN

- Lesions less than 1 cm diameter may be missed.
- Lesions with attenuation similar to that of bone may be missed if near the skull.
- Lesions with attenuation similar to that of brain are poorly imaged such as plaque of multiple sclerosis, subdural hematoma.
- CT sometimes misses lesions within the posterior fossa (therefore imaging of choice for posterior fossa lesion is MRI).
- The spinal cord is not imaged directly without contrast.
- Requires cooperation of patient.

MAGNETIC RESONANCE IMAGING (MRI)

MRI can detect brain tumors, infarction, hemorrhage and lesion of posterior fossa. In the spinal cord MRI shows tumors, syringomyelia cord compression and vascular malformations.

ADVANTAGES OF MRI (compared to CT)

- MRI can select any plane, e.g. coronal, sagittal and oblique.
- No ionizing radiations.

- More sensitive to tissue changes e.g. plaques of demyelination (multiple sclerosis) are seen.
- No bone artifacts.
- Spinal cord and nerve rots are imaged directly (no contrast required).
- Lesion less than 0.5 cm are seen.
- Magnetic resonance angiography (MRA) images blood vessels without need of contrast.

LIMITATIONS OF MRI

- It takes time
- Expensive
- Needs patient's cooperation
- Claustrophobia-fear of confined space of an MRI tube.

ELECTROENCEPHALOGRAPHY (EEG)

EEG is the recording of the electrical activity of the cerebral cortex obtained with 16 electrodes applied to the skull at various points simultaneously for 10-30 minutes. The main value of EEG is in diagnosing epilepsy and diffuse brain diseases. However patient with epilepsy often have a normal EEG in between seizures.

- **Epilepsy:** spikes, or spikes-and- wave abnormalities are the hallmark of epilepsy.
- **Diffuse brain disorders:** generalized slow wave EEG pattern appears in encephalitis, dementia and metabolic encephalopathies (e.g. hypoglycemia, hepatic encephalopathy)
- **Brain death:** EEG is isoelectric in deep coma and death.

ELECTROMYOGRAPHY (EMG)

A concentric needle electrode is inserted into voluntary muscle. The amplified recording is viewed on an oscilloscope. Three main features can be demonstrated:

- A normal pattern
- Denervation and re-innervation
- Myopathic, myotonic, or myasthenic changes.

NERVE CONDUCTION STUDIES

Nerve conduction studies help in diagnosing neuropathies and nerve entrapment.

Distal latency (latency from stimulus to recording electrodes), ***amplitude*** of the evoked response and ***conduction velocity*** all provide information on motor and sensory nerve.

Nerve conduction velocity (NCV) slows with age, fall in body temperature and pathologically with nerve entrapment (e.g. carpal tunnel syndrome), demyelinating neuropathy (e.g. Guillain barre syndrome) and multifocal motor neuropathy.

CEREBRAL -EVOKED POTENTIALS

Visual evoked potential record the time for a visual stimulus to reach the occipital cortex. Their value is chiefly in demonstrating previous retrobulbar neuritis which leaves a permanent delay in latency despite recovery of vision. Evoked potentials can be measured following auditory or somatosensory stimuli.

BIOPSY

Brain

CT-guided biopsy of intracranial mass is now a standard procedure.

Muscle

Biopsy with light microscopy or biochemical analysis is helpful in diagnosing inflammatory, metabolic and dystrophic disorders of muscle.

Peripheral nerve

Biopsy, usually of sural nerve at the ankle aids diagnosis in certain neuropathies (e.g. due to vasculitis).

CSF ANALYSIS

Described in the section of meningitis.

CSF PARAMETERS IN HEALTH AND SOME COMMON DISORDERS						
	Normal	Subarachnoid hemorrhage	Acute bacterial meningitis	Viral meningitis	Tuberculous meningitis	Multiple sclerosis
Pressure	50-180 mm of water	Increased	Normal/increased	Normal	Normal /increased	Normal
Color	Clear	Blood –stained xanthochromic	Cloudy	Clear	Clear/cloudy	Clear
RBC	0-4/mm^3	Raised	Normal	Normal	Normal	Normal
WBC	0-4/mm^3	Normal/slightly raised	1000-5000 neutrophils	10-2000 lymphocytes	50-5000 lymphocytes	0-50 lymphocytes
Glucose	> 60% of blood level	Normal	Decreased	Normal	Decreased	Normal
Protein	<0.45 g/L	Increased	Increased	Normal/increased	Increased	Normal/increased
Microscopy	Sterile	Sterile	Organisms on Gram stain and/or culture	Sterile/virus detected	Ziehl-Neelsen stain positive	sterile
Oligoclonal bands	Negative	Negative	Can be positive	Can be positive	Can be positive	Often positive

MENINGITIS

Meningitis is an inflammation of meninges caused by bacteria, mycobacteria, fungi, spirochetes, protozoa and helminthes.

CAUSES OF MENINGITIS
Bacteria
Neonates (less than 1 month) • Gram negative bacilli (E. coli, proteus etc) • Group B streptococci • Listeria monocytogenes (less common) **Pre-school child (1 month to 6 years)** • H. Influenzae • Neisseria meningitides • Streptococcus pneumoniae • Mycobacterium tuberculosis **Older child and adults** • Neisseria meningitides • Streptococcus pneumoniae • Listeria monocytogenes • Mycobacterium tuberculosis • Staph. aureus, H. influenza

Viruses	Protozoa and other parasites
• Enteroviruses (echo, Coxsackie, polio) • Mumps • Influenza • Herpes simplex • Varicella zoster • Epstein-Barr • HIV • HIV • Lymphocytic choriomeningitis	• Toxoplasma • Amoeba • Cysticercus **Fungi** • Cryptococcus neuformans • Candidiasis • Histoplasma • Blastomyces • Coccidiodes • Brucella • Sporothrix

Common features of meningitis

1. *Features of infection:*
   Fever, rigor, leukocytosis
2. *Features due to raised intracranial pressure:*
   Headache, nausea, vomiting, deterioration of consciousness and convulsions.
3. *Features of meningeal irritation:*
   Neck rigidity, positive kerning's sing, photophobia

ACUTE BACTERIAL MENINGITIS

Acute bacterial meningitis is an inflammatory response to bacterial infection of pia-arachnoid matter and CSF of subarachnoid space. It is one of the common medical emergencies.

EPIDEMIOLOGY

The incidence of bacterial meningitis is 5-10 in 100000 annually in developed countries. The incidence may be higher in Pakistan.

ETIOLOGY

The etiologic agent of meningitis varies according to the age of the patient.

- *Menigococcus* (Neisseria meningitides) is the most common cause of meningitis, spread is by air- borne route. The organism invades through nasopharynx producing septicemia usually associated with meningitis.
- In *pneumococcal and H. influenzae* infection there may be an associated otitis media. Pneumococcal meningitis may be associated with pneumonia and nonfunctioning spleen.
- *Listeria monocytogenes* causes meningitis in immunosuppressed, diabetics, alcoholics, pregnant women, neonates and elderly.

PATHOLOGY

The pia-arachnoid matter is congested and infiltrated with inflammatory cells. A thin layer of pus forms and this may later organize to form adhesions leading to obstruction to free flow of CSF and hydrocephalus formation. Cranial nerve damage may occur at the base of brain. Pneumococcal meningitis is often associated with very purulent CSF and high mortality

ORGANISMS OF MENINGITIS ACCORDING TO AGE

Organisms	Neonates (< 1 month) %	Children (1 month to 15 years) %	Adults (>15 years) %
N. meningitides	0-1	25-40	10-35
S. pneumoniae	0-5	10-20	30-50
H. influenzae	0-3	40-60	1-3
Gram –ve bacilli	50-60	1-2	1-10
Streptococci	20-40	2-4	5
Staphylococci	5	1-2	5-15
Listeria	2-10	1-2	5

These are American figures where S. pneumoniae is the commonest cause of meningitis in adults while in Pakistan N. meningitides is more common.

Meningococcal meningitis

This type of meningitis occurs in children and young adults, mostly during winter season by the organism called Neisseria meningitides (meningococci). It is a bean-shaped gram –ve diplococcus which inhabits nasopharynx and is transmitted by respiratory secretions.

- Incubation period is 1-5 days.
- Meningitis due to N. meningitides may occur in epidemics.
- Carrier having organism in nasopharnx are the principal source of transmission.
- Predisposing factor may be complement deficiency (C5 to C8 and perhaps C9).
- **Meningococcemia** is a fulminant form of septicemia without meningitis presenting with petechial rash often first appearing in the lower extremities, size of petechiae varies from pin-head to large echymosis. Therefore it should be noted that patient with meningococcus infection may present with meningitis, meningococcemia or in combination of both.

S. Pneumoniae meningitis

Predisposing factors for streptococcal pneumoniae meningitis are pneumonia otitis media, sinusitis, endocarditis, splenectomy, cirrhosis, alcoholism and head trauma with basilar skull fracture. In the United States it is the most common cause of meningitis in adults, however in Pakistan N. meningitides is more common.

H. Influenzae meningitis

- Nearly all cases of H. influenzae meningitis occur in children under 6 years of age.
- Predisposing factors are sinusitis, epiglottitis, pneumonia, otitis media, head trauma, diabetes and immunodeficiency such as AIDS.

Listeria monocytogenes meningitis

Meningitis due to L. monocytogenes is more likely in neonates, elderly, alcoholics, diabetics and cancer patients.

Meningitis due to gram negative bacilli

Meningitis due to gram-negative bacilli occurs in extremes of life (i.e. neonates and elderly). E.coli is isolated in 30-50% cases of bacterial meningitis in neonates.

CLINICAL FEATURES OF ACUTE BACTERIAL MENINGITIS

Symptoms

- Abrupt onset with headache, vomiting, fever
- Pain and stiffness in neck & back
- Muscular rigidity (neck rigidity)
- Altered level of consciousness such as confusion, delirium, lethargy and coma. It is important to note that in uncomplicated meningitis consciousness is not much impaired, although the patient may be delirious due to high-grade fever. Progressive drowsiness, cranial nerve palsy and focal neurological deficits indicate complications such as severe cerebral edema or hydrocephalus, or an alternative diagnosis such as cerebral abscess or encephalitis.

Signs

Neck rigidity:
Inflammation of meninges due to infection evokes reflex spasm in the paravertebral muscles. This spasm results in neck stiffness (or rigidity) in the cervical area, while in the lumber area muscle spasm may produce a positive Kerning's sign.

Kerning's sign:
Flex the hip at 90 degree and try to extend the leg at knee; the patient feels pain due to the spasm of hamstrings muscles.

Brudzinki's sign:
Spontaneous knee and hip flexion when neck flexion is attempted is called Brudzinski's sign.

Note: Kernig's and/ or Brudzinski's signs are present only in about 50% cases in adults and their absence does not rule out the diagnosis of bacterial meningitis.

Rash
In about 50% patients with meningococcemia purpuric or petechial rash develops principally on the extremities.

FEATURES OF MENINGOCOCCAL SEPTICEMIA

- Meningitis
- Rash
- Shock
- DIC
- Renal failure
- Peripheral gangrene
- Arthritis (septic or reactive)
- Pericarditis (septic or reactive)

Features of complications

- Deteriorating level of consciousness.
- Cranial nerve palsies especially involving IV, VI, and VII are found in 10-20% of cases. Bilateral VI nerve palsy suggests raised intracranial pressure (ICP).
- Focal neurological deficits such as dysphasia and hemiparesis may be present.
- Seizures occur in about 40% of cases and are more common with S. pneumonia as compared to H. influenzae or N. meningitides.

  Features of raised ICP such as hypertension, bradycardia, third nerve palsy and coma may be present.

Features in elderly

In elderly meningitis is often has an incidious onset with lethargy or obtundation with variable signs of meningeal irritation and no fever. Therefore in elderly altered mental status should be considered due to meningitis until proved otherwise.

Features in neonates

Classic signs and symptoms of meningitis may be absent in neonates. Neck rigidity and / or fever are commonly absent. Babies present with restlessness, high-pitched crying, refusal to feed and irritability.

COMPLICATIONS

Septicemia, DIC and shock
Organisms may settle in tissues such as lungs, bones, joints or eyes causing local infection.

Neurological:
- Raised ICP and / or diffuse cerebral edema leading to:
  - Cranial nerve palsies
  - Focal neurological deficits (e.g. deafness, blindness).
  - Seizures.
  - Encephalopathy
  - Subdural effusion.
- Obstructive hydrocephalus due to adhesions
- Behavioral disturbances and mental retardation.

Septic arthritis
May be early due to septicemia or late due to immune reaction.

Syndrome of Inappropriate ADH Secretion
SIADH causes hyponatremia

Infarction of adrenal gland
It is one of the complications of meningococcal septicemia.

DIFFERENTIAL DIAGNOSIS
- Viral meningitis
- Tuberculous meningitis
- Other types of meningitis
- Encephalitis
- Brain abscess
- Subarachnoid hemorrhage
- Cerebral malaria
- Brain tumor
- Meningism

MENINGISM
Meningism means meningeal irritation in the presence of normal CSF

Cause:
1. Typhoid fever
2. Apical pneumonia
3. Shigellosis
4. Acute exanthemia
5. Pyelonephritis
6. Cervical lymphadenopathy

INVESTIGATIONS

Lumber puncture
The CSF findings in bacterial meningitis are:
- Elevated opening pressure
- Increased cell count (> 1000/mm) with predominant polymorph leukocytes.
- Elevated protein concentration (> 150mg/dl) due to disruption of blood brain barrier and/ or generation of proteins by leukocytes and microorganisms in subarachnoid space.
- Low glucose concentration (<40mg/dl) or less than 60% of blood glucose).
- Gram stain of CSF identifies etiological agent in 60-90% cases of bacterial meningitis.
- CSF culture is positive in 70-85% and should be sent even there is no leukocytosis in CSF.
- CSF polymerase chain reaction (PCR) may help in the diagnosis of bacterial meningitis.
- Prior antibiotic therapy reduces the yield of CSF gram stain and culture but the cell count, protein and glucose are not altered for several days.

Blood culture
Blood culture may be positive even when the CSF culture is negative.

Blood CP
Blood CP shows neutrophilic leucocytosis.

Coagulation screen and fibrin degradation product analysis
PT, APTT, platelets and fibrin degradation product (FDP) should be performed to rule out DIC.

Serum urea, creatinine and electrolytes
Required to assess the renal status, there will be hyponatremia in case of SIADH.

X-ray chest.
To identify the source of infection.

CT scan of brain
CT is performed if mass lesion is suspected.

CSF FINDINGS IN MENINGITIS					
Condition	**Cell type**	**Cell count**	**Glucose**	**Protein**	**Gram stain**
Normal	Lymphocytes	0- 4/mm^3	> 60% of blood glucose	Up to 45mg/dl	-
Viral	Lymphocytes	10-2000	Normal	Normal	-
Bacterial	Polymorphs	1000-5000	Low	Elevated	+
Tuberculous	Polymorphs/ Lymphocytes/ mixed	50-5000	Low	Elevated	Often –ve
Fungal	Lymphocytes	50-500	Low	Elevated	+
Malignant	Lymphocytes	0- 100	Low	Normal/elevated	-

MANAGEMENT

General

1. Bed rest
2. I/V fluids to prevent dehydration, fluid restriction if seizure develop, maintenance of fluid electrolyte balance.
3. Airway patency.

Initial antimicrobial therapy

Bacterial meningitis may prove fatal within hours; successful treatment depends an early diagnosis, and I.V. administration of appropriate antibiotics (that can cross blood brain barrier) in an anti-meningitic does until the causative organism and its antibiotic sensitivity have been identified . If the cause of meningitis is not clear, antimicrobials are selected on the basis of clinical setting, age of the patient and the Gram stain. Antibiotics should be started as soon as possible even by general practioner as he suspect meningitis.

<u>Patient with a typical meningococcal rash</u>
Benzylpenicillin 24 million units/24 hours

<u>Adults aged 18-50 years without typical meningococcal rash</u>
Third generation cephalosporin such as ceftriaxone (Rocephin) 2 gm IV 12 hourly or 4g once a day, or cefotaxine (Claforan) 2 gm 6 hourly is advised while the culture results are awaited.

Ceftriaxone should be avoided in neonates due to its albumin binding and interference in biliribun metabolism in this age group.

TREATMENT OF PYOGENIC MENINGITIS OF UNKNOWN CAUSE

Neonate
- Ampicillin with cefotaxime or gentamicin

Infant
- Ampicillin with cefotaxime

Pre-school child
- Ceftriaxone

Older child and young adult
- Penicillin G and ceftriaxone

Older patient (> 50 years)
- Ampicillin with ceftriaxone

SPECIFIC THERAPY IF ORGANISM IS KNOWN		
Organism	**Antibiotic**	**Alternative**
Meningococcus	Benzyl penicillin	Ceftriaxone
S. pneumoniae	Ceftrixone Add vancomycin or rifampicin in resistance to β-lactum	Benzyl penicillin
H. influenza	Ceftriaxone	Chloramphenicol
Listeria	Ampicillin + gentamicin	Co-trimoxazole
G –ve bacilli	Ceftriaxone/ cefotaxime	Ampicillin+ Gentamicin

Benzyl penicillin 4 millions units IV 4 hourly Ampicillin 2 g IV 4 hourly.

Duration of therapy.	
Organism	*Duration*
Meningococcus	7 days
S. pneumoniae	10-14 days
H. influenza	7-10 das
G –ve bacillie	3 weeks

Adjunctive therapy

Mannitol
Patients with raised intracranial pressure due to cerebral edema may get benefit from elevation of the head of the bed to 30 degree and mannitol 250 ml I/V bolus over a period of 1-2 hours. Dexamethasone (Decadrone) 4 mg I/V 6 hourly may also reduce the cerebral edema.

Glucocorticoids
Dexamethasone therapy is very effective in children and reduces the incidence of hearing loss and other neurological deficits but in adults its role is controversial. However it should be given in adults especially in patients with positive Gram -stain, raised ICP or altered mental status. Dosage is 0.15 mg/kg IV 6 hourly.

Anti-epileptics
If patient has seizure activity, diazepam and/ or phenytoin may be used. Barbiturates may be needed.

Prophylaxis of meningococcal infection
Household and other close contacts of patients with meningococcal meningitis should be given 2 days of oral rifampicin 600 mg 12 hourly for adults and 10mg/kg for children.
Ciprofloxacin (Tab. Novidate) 500 mg as a single dose in adults is an alternative.

Vaccination
Vaccines are available for prevention of disease caused by meningococci of group A and C (not effective for group B).

Prognosis
The mortality rate is 5-10%

TUBERCULOUS MENINGITIS (TBM)

Tuberculous meningitis (TBM) may occur due to rupture of a meningeal tuberculoma resulting from earlier hematogenous seeding of tubercle bacilli from a pulmonary focus, or it may develop as a consequence of miliary (disseminated) tuberculosis. In about 75% of cases evidence of tuberculosis outside the nervous system, most frequently in the lung can be found.

TBM is more marked at the base of the brain and thick exudates often involves cranial nerves causing cranial nerve palsies.

- (TBM is a very common long case in medicine viva)

CLINICAL FEATURES

- Mostly gradual onset sometimes presents acutely.
- When onset is gradual it presents as low-grade fever, anorexia, and irritability followed by headache, vomiting, confusion, neck stiffness, convulsion and coma.
- In older patients headache and behavioral changes are prominent early symptoms.
- The initial manifestation of the patient may be hemiplegia, cranial nerve palsy (mostly oculomotor) or coma.
- Opthalmoscopy may reveal choroids tubercle when there is associated miliary tuberculosis.

CLINICAL FEATURES OF TUBERCULOUS MENINGITIS	
Symptoms	**Signs**
• Headache	• Meningism (may be absent)
• Vomiting	• Oculomotor palsies
• Low-grade fever	• Papilloedema
• Lassitude	• Depression of conscious level
• Depression	• Focal hemisphere signs
• Confusion	
• Behavioral changes	

INVESTIGATIONS

Lumbar puncture:

CFS examination shows:

- Pressure is raised
- *Necked eye examination:* fluid is clear or slightly haziness may be present due to increased protein content. When CSF is allowed to stand, there is formation of a fine clot (cob-web).
- Proteins are raised (100-500 mg/dl)
- Sugar is decreased
- Chloride is normal.

- Microscopy: shows 100-500 WBC/mm mainly lymphocytes, initially polymorph may dominate.
- AFB-stain shows bacilli in less than one third of patients.
- CSF culture for AFB may be negative in 15-25% of cases, AFB culture requires 6-8 weeks.
- CSF polymerase chain reaction (PCR) is helpful for identification of mycobacterial DNA.

CT scan

CT scan may show hydrocephalus and abnormal enhancement of basal cisterns or ependyma. CT contrast may show **tuberculoma** as ring lesion (an uncommon manifestation of tuberculosis, presents as one or more space- occupying lesions and usually causes seizures and focal signs such as hemiplegia, paraplegia, cranial nerve palsy).

Chest x-ray

Chest x-ray mostly shows features of tuberculosis but it may be normal.

COMPLICATIONS

1. Hydrocephalus
2. Mental retardation
3. Cranial nerve palsies
4. Hemiplegia
5. Blindness
6. Epilepsy

TREATMENT

Anti-tuberculous therapy (ATT)

Treatment should be given for 12 months. For initial 2 months all four drugs are given after 2 months pyrazinamide is withdrawn and other 3 drugs are given for 10 months.

- Isoniazid 5 mg/kg/day single dose (max. 300mg).
- Rifampicin 10mg/kg/day single dose (max. 600mg).
- Pyrazinamide 15-30 mg/kg/day single dose (max. 2 g)
- Ethambutol 25mg/kg/day single dose (max. 2.5 g).
- Pyridoxine (Vit. B6) 50 mg/daily.

Steroids

Steroids may reduce the inflammatory reaction and thereby decrease the incidence of obstructive hydrocephalus. Initially start with dexamethasone 0.2 mg/kg 6-8 hourly IV for 1-2 weeks to reduce the raised intracranial pressure and then orally 2mg/kg prednisolone in tapering doses up to 3 weeks.

Surgical intervention

Surgical treatment as ventriculoatrial or ventriculoperitoneal shunt may be required in case of severe hydrocephalus not responding to early medical treatment; main complication of shunt are infection and blockage.

VIRAL MENINGITIS

ETIOLOGY

Coxsackie, mumps, measles, hepatitis virus, infectious mononucleosis, herpes zoster and AIDS viruses are commonly responsible.

CLINICAL FEATURES

1. Mostly younger patient
2. Acute onset
3. Fever, headache, neck stiffness and vomiting
4. Signs of meningeal irritation present.

INVESTIGATIONS

CSF examination
- Pressure is raised
- Slight haziness is present
- Proteins are slightly raised (not more than 200mg/dl).
- Glucose normal (important D/D finding from bacterial meningitis), but may be low in herpes simplex meningitis.
- Chloride – normal.
- Microscopic examination shows 10-2000/μL mostly lymphocytes. Initially neutrophils may be predominant but within 12-24 hours lymphocytes predominate.

TREATMENT
- No specific treatment for viral meningitis because it is a self-limiting disease.
- Bed rest, analgesics, and maintenance of water electrolyte balance are basic steps to be undertaken. Recovery usually occurs within days.

ENCEPHALITIS

Encephalitis is an inflammation of brain parenchyma. It is caused mainly by a variety of viruses & also occurs in bacterial & other infections. Frequently there is concomitant meningitis, so the disease is usually meningoencephalitis. It is a common medical emergency.

VIRAL ENCEPHALITIS
The most common cause of viral encephalitis is herpes simplex virus, which probably reaches the brain via the olfactory nerve.

DIFFERENTIAL DIAGNOSIS OF VIRAL ENCEPHALITIS

- Acute metabolic encephalopathy
- Cerebral tumor
- Stroke
- Bacterial meningitis
- Brain abscess
- Tuberculous meningitis

CAUSES OF VIRAL MENINGITIS AND ENCEPHALITIS

- Herpes simplex virus
- Enteroviruses (Echoviruses, coxsackieviruses, polioviruses).
- Mumps virus
- Influenza virus
- Japanese encephalitis virus
- Arboviruses
- Togaviruses (e.g. yellow fever)
- Bunyaviruses (e.g. sandfly fevers)
- Rabies virus
- Human immunodeficiency virus
- Lymphocytic choriomeningitis virus (arenavirus).

Clinical features
1. Acute onset of headache & fever, meningism and drowsiness in mild cases.
2. In severe illness focal signs (e.g. aphasia, hemiplegia or cranial nerve palsies), seizures and coma develop.
3. Altered consciousness, focal signs and seizure are more common in encephalitis as compared to meningitis.
4. Patient may be agitated (while in meningitis patient is usually calm, conscious, drowsy and non- agitated)

Investigations
1. **CT scan:** shows areas of edema, in herpes simplex encephalitis CT scan may show low density lesions in the temporal lobes.
2. **EEG**: shows slow wave changes
3. **CSF examination:** It should be preceded by CT scan to exclude a mass lesion (such as brain abscess) because there may be risk of brain herniation. CSF shows excess lymphocytes, but neutrophils may predominate in the early stages. Protein may be elevated but the glucose is usually normal.
4. **Viral serology** of blood & CSF
5. **PCR**: herpes simplex virus DNA can be detected by PCR.

Investigations in viral encephalitis
- Full blood count/metabolic screen
- Viral studies
- CT scan (MRI scan)
- CSF examination
- Electroencephalogram

Treatment
1. Nursing of unconscious patient as described in stroke.
2. Dexamethasone 4 mg Q.I.D. for raised intracranial pressure.
3. Acyclovir (Inj. Zovirax 250mg) 10mg/kg I/V 8-hourly for herpes simplex virus (Acyclovir should be given to all suspected cases of viral encephalitis).
4. Anticonvulsants: if epilepsy develops.

Prognosis
- Mortality is 10-30% when antiviral drugs are used, without antiviral mortality is 70%.
- Survivors may have cognitive impairment or develop epilepsy.

LUMBER PUNCTURE

Indications

Diagnostic
- Meningitis
- Encephalitis
- Guilian-Barre syndrome
- Transverse myelitis
- Benign intracranial hypertension
- Unexplained neurologic disorders such as:
  Seizure
  Stroke
  Altered level of consciousness

Therapeutic
Intrathecal administration of antibiotics or anti-neoplastic agents.

Consent
Describe the whole procedure, its advantages and risk factors to the patient or attendant and take a written consent for the procedure.

Position of the patient
- The patient is asked to lie on his/her side facing away from the examiner.
- The back is positioned at the edge of the bed.
- The patient is asked to roll up into a ball - the neck is gently flexed and the knees drawn up to the abdomen. Proper position is essential for success.

Site of needle insertion
As the spinal cord terminates at L1 vertebral level, the puncture is performed below this level i.e. between L3-L4 or L2-L3. Posterior iliac crest corresponds to the L3-L4 interspace and is a useful anatomical landmark.

Cleaning of area and local anesthetic
The area is draped and cleaned by multipl washings with antiseptic lotion such as pyodine Local anesthetic, 1% Lignocaine is injected into th subcutaneous tissues.

Procedure
After 5 minutes of injection, the lumber puncture needle (20 or 22 gauge) is inserted in the midline between two spinous process and slowly advanced to the direction of umbilicus. In adults, the needle is advanced 4-5cm before the subarachnoid space is reached, and the examiner usually recognizes entry as a sudden release of resistance. Then stylet is removed and the needle is attached to the manometer to measure pressure. Then fluid is collected for:
- CSF D/R (including cell count, glucose protein).
- Gram stain/AFB stain.
- CSF cytology
- CSF culture and sensitivity

Problems
Dry tap
There is no fluid even the needle is in subarachnoid space if there is a block at a higher level or the lumber sac is filled with neoplastic tissue. Sometimes changing the position of needle results in flow of CSF.

Hemorrhagic tap
Puncture of meningeal vessel or subarachnoid hemorrhage causes blood stained fluid. To differentiate take 2-3 ml fluid in 3 bottles. In subrachnoid hemorrhage fluid will be uniformly stained while in traumatic tap CSF clears in the third bottle.

Contraindications.

- Raised intracranial pressure- as it can lead to cerebellar or tentorial herniation. If fluid is required, CT scan is obtained to exclude mass lesion. Raised ICP manifests as
  - Papilloedema
  - Deteriorating level of consciousness
  - Focal neurological deficit (e.g. hemiplagia, dysphasia, cranial nerve palsies).
- Gross spinal lesion, skin or soft tissue infection

Particular care is required in patients of thrombocytopenia or disorders of blood coagulation.

BRAIN ABSCESS

PREDISPOSING FACTORS

- **Direct spread** of organism from a skull fracture or a focus of infection in the paranasal sinuses or middle ear, mostly involving the frontal and temporal lobes.

- **Haematogenous spread** can occur from any site of primary infection, but is commonly associated with:
  - Infection of chest, including lung abscess bronchiectasis, and empyema (most commonly).
  - Infection of heart such as endocarditis
  - Infection of bone or dental abscess can be primary site of infection.

ETIOLOGY

Mixed aerobic and anaerobic organisms are involved in brain abscess. The most common organisms are:

- Streptococcus melleri
- Bacteroides
- Enterobacteriae
- Staphylococcus

SITE., SOURCE AND ORGANISMS IN CEREBRAL ABSCESS

Site of abscess	*Source of infection*	*Likely organism*
Frontal	Frontal sinusitis	Streptococcus
Temporal	Otitis media	Streptococcus Bacteroides Proteus
Cerebellar	Otitis media	Streptococcus Bacteroides Proteus
Parietal	Embolic	Streptococcus Bacteroides Proteus
Any site	Trauma	Staphylooccus

CLINICAL FEATURES

The illness develops more gradually than acute bacterial meningitis, but 75% of cases seek medical attention within 2 weeks of onset of symptoms.

- Headache, drowsiness and confusion are early symptoms.
- Later on signs of raised ICP, seizure and focal neurological deficits (such as hemiplegia) develops.

INVESTIGATIONS

Blood CP/ESR
Blood CP shows leukocytosis and there is raised ESR.

CT scan brain
CT scan of brain shows single or multiple low-density areas, which enhance peripherally with contrast to provide the *ring appearance* with central low density and surrounding cerebral edema.
(Note: similar abnormality on CT may be seen due to metastatic tumor).

Lumber puncture
Lumber puncturer is contraindicated de to raised ICP and CSF findings are not helpful in diagnosis.

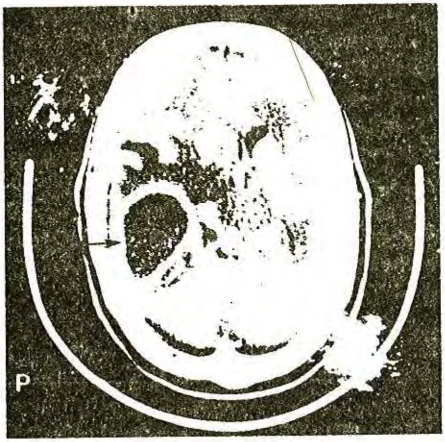
MANAGEMENT

Antibiotics

- Inj. Benzyl penicillin 2million units IV hourly PLUS
- Inj. Chloramphenicol (1gm) 1-2 g IV 6 hourly PLUS
- Inj. Metronidazole (Flagyl) 500mg IV 6 hourly

Steroids

- Inj. Dexamethasone (Decadrone 4mg and 8mg) 4-25 mg 6 hourly followed by tapering of the dose to reduce the cerebral edema.



POLIOMYELITIS

ETIOLOGY

Type I, II & III Polio virus. These viruses have marked propensity for the nervous system, especially the anterior horn cells of lumbar segment of spinal cord. Spread is via oro-fecal route.

CLINICAL FEATURES

- Incubation period: 10-14 days.
- It is a disease of children, but no age is exempt
- Following are the clinical presentations:

1. *Inapparent infection* is common and occurs in 95% of infected individuals.
2. *Abortive poliomyelitis:*_(4-5%) characterized by fever, sore throat and myalgia. The illness is self-liiting & of short duration.
3. *Non-paralytic poliomyelitis* is characterized by fever, sore throat, myalgia and signs of meningeal irritation, but recovery is complete.
4. *Paralytic poliomyelitis:*_(0.1%) initial features are fever, headache, sore throat & myalgia which subside in 4-5 days & then recur with neck stiffness & muscle pain in neck & lumbar region. These symptoms persist for a few days followed by the onset of asymmetrical paralysis usually confined to lower limbs in children under 5 years of age & upper arm in older children, whereas in adults it manifests as paraplegia or quadriplegia.

- Respiratory failure may occur if intercostals muscles are paralyzed.

DIAGNOSIS:

On clinical bases

MANAGEMENT

1. Complete bed rest is essential in early course of disease, exercise at this stage predispose to paralysis.
2. If respiratory difficulty – tracheostomy & intermittent positive pressure ventilation.
3. Once the acute phase has subsided, subsequent treatment is by physiotherapy & orthopedic measures.

RABIES (Dog bite)

Rabies is caused by a rhabdovirus which infects the CNS and salivary glands of a wide range of mammals, and is usually conveyed by saliva through bites or licks on abrasions. Biting animals may be dogs, cats, foxes or bats; rodents ant rabbits are unlikely to have rabies. It is a major risk to public health and therefore a common topic for exams.

Incubation period 3-7 weeks usually – may be 10 days to several years. The interval depends on distance of the wound from the CNS because the virus travels in the nerves to brain.

CLINICAL FEATURES

Only a proportion of people bitten by a rabid animal develop the disease, but once manifest it is almost invariably fatal.

- Fever & paraesthesia at the site of bite at the onset of the illness.
- Increasing anxiousness
- *Hydrophobia:* although the patient is thirsty, attempt at drinking provokes violent contraction of the diaphragm and other respiratory muscles and therefore even sight or sound of water may precipitate distressing laryngeal spasm and attacks of panic.
- *Air currents:* skin becomes sensitive to changes of temperature, especially air currents. Therefore if you blow on patient's face he becomes scared.
- *CNS involvement*: About 10 days later CNS involvement begins in an encephalitic form manifesting as delusion, hallucination accompanied by spitting, biting and mania. The less common presentation is paralytic form in which ascending paralysis occurs resembling Guillain- Barre syndrome.
- Cranial nerve lesions develop.
- Terminal hyperpyrexia, coma and autonomic dysfunction lead to death despite intensive support.

INVESTIGATIONS

- Biting animals should be kept under observation for 7-10 days; usually they die within 5-7 days. Brain of the animal is examined for rabies by the fluoresencent antibody technique.
- When the animal cannot be examined they must be assumed to be rabid.
- PCR of CSF or saliva may be performed as definitive diagnosis assay.

TREATMENT

Local treatment of animal bite

Thorough cleansing, debridement and repeated flushing of wound with soap and water are important. Wound should not be sutured. If the rabies immunoglobulin or antiserum is to be given, a portion should be infiltrated locally around the wound and remainder given intramuscularly.

Symptomatic patient

- No treatment, poor survival rate, death occurs in 5-7 days after onset of symptoms due to respiratory failure.
- Sedate the patient with diazepam 10 mg 4-6 hourly plus chlorpromazine 50-100 mg.

PREVENTION

Vaccination of animal is the important preventive measure for rabies.

Post-exposure prophylaxis

1. Wound should be thoroughly cleaned with soup, damaged tissues should be excised and the wound left unsutured.
2. Rabies immune globulin (Bayrab) 2ml contains 300 IU) – dosage is 40 units/kg 50% infiltrated around the wound. (Cost > Rs. 6000)
3. If immune globulin (Human) is not available equine rabies antiserum (ARV) 20 units/kg can be used after test dose for horse serum sensitivity.
4. Vaccine: an inactivated human diploid cell rabies vaccine (Verorab) is given as five injections of 1ml IM in deltoid on day 0, 3, 7, 14, and 28 after exposure.
5. When human vaccine is not present or when risk of rabies is slight (licks' on the skin, or minor bites of covered arm or legs) treatment can be delayed upto 5 days while observing the biting animal. If it is healthy after 5 days, it does not have rabies, if it dies, escapes or is killed then treatment should be continued.

Pre-exposure immunization

Pre-exposure prophylaxis with three injections of diploid cell vaccine IM 1ml on days 0, 7, 21, 28 is recommended for persons at high risk of exposure.

SEIZURES AND EPILEPSY

A *Seizure* is an abnormal clinical event caused by an abnormal and excessive electrical discharge from the cerebral neurons.

The term seizure and epilepsy are not synonymous; *epilepsy* is a tendency to have seizures and is defined as a condition in which a person has recurrent seizures due to chronic underlying process.

A person with a single seizure or recurrent seizures due to correctable or avoidable circumstances does not necessarily have epilepsy. A single seizure is not epilepsy but an indication for investigation to identify the cause.

ETIOLOGY

Epilepsy has several causes that are usually related to the age of the patient. About 70-90% of epileptic patients have their first seizure before the age of 20.

Epilepsy may be primary or idiopathic which predominantly reflects genetic predisposition or it may be secondary in which seizures result from a known structural or metabolic disease of the brain.

IDIOPATHIC OR PRIMARY EPILEPSY

In this type of epilepsy seizures usually begin between 5 and 20 years of age but may start later in life. No specific cause can be identified, and there is no other neurological abnormality. If patient develops seizures first time after age 20 it must be considered due to some underlying cause (secondary epilepsy).

SECONDARY EPILEPSY

Causes of secondary epilepsy may be the following.

Genetics
Congenital abnormalities and perinatal injuries.

Metabolic disorders
- Hyperglycemia
- Hypoglycemia
- Hepatic failure, renal failure

Head injury, birth injury
Tumors and other space occupying lesions.

Vascular diseases
Stroke, AV malformation,

Infections
Meningitis, encephalitis, cerebral abscess, AIDS, tuberculosis.

Inflammatory diseases
SLE, multiple sclerosis, sarcoidosis, vasculitis

Drugs
Penicillin, isoniazid, metronidazole, quinolones, cyclosporine, lithium, antidepressants, antipsychotics, theophyline, amphetamine, cocaine.

Withdrawal of sedative hypnotics
Alcohol, barbiturates, benzodiazepines.

PRINCIPAL CAUSES OF SEIZURES BY AGE OF ONSET	
Neonatal	Developmental insufficiency or brain injury
Infantile	Congenital malformations, perinatal injury, metabolic disorders
Children and adolescents	Mainly genetic
Adults over 20	Some genetic otherwise cerebral neoplasm, drug or alcohol withdrawal, brain trauma, stroke, infection or surgery.

CLASSIFICATION OF SEIZURES

Seizures are classified broadly into two groups:

- *Partial or focal seizures* are those in which the seizure activity is restricted to one part of the cerebrum i.e. there is focus of increased electrical activity in one hemisphere.
- *Generalized seizures* are those involving diffuse regions of both hemispheres simultaneously and synchronously.

As a rule, partial seizures are typically associated with structural abnormalities of the brain such as scars, tumors, AV malformations, or focal areas of inflammation. In contrast, generalized seizures may result from cellular, biochemical or structural abnormalities that have a more widespread distribution.

CLASSIFICATION OF EPILEPSY

Partial seizures
- Simple-partial seizures (no impairment of consciousness) e.g. Jacksonian seizures.
- Complex- partial seizures (with impairment of consciousness) e.g. psychomotor epilepsy.
- Partial seizures evolving to generalized seizures (also called secondary generalized seizures).

Generalized seizures
- Absence (petitmal) seizures
  - Typical absence
  - Atypical absence
- Myoclonic seizures
- Tonic-clonic (Grandmal) seizures
- Atonic seizures

PARTIAL SEIZURES

They start by activation of group of neurons in one part of one hemisphere. They are also called focal seizures.

Simple partial seizures

In this condition consciousness is preserved. It may present with motor, sensory, autonomic or psychic symptoms as following:

Partial motor seizures

There may be three patterns in partial motor seizures:

1. *Jacksonian march:* Jerky movements typically begin in a very restricted region such as at the angle of the mouth or in the thumb and index finger, spreading to involve the whole limb within seconds or minutes. The clinical evidence of this spread of activity is called the "march of seizure" representing the spread of seizure activity over a progressively larger region of motor cortex.
2. *Todd's paralysis:* Some patients may experience a localized paresis for minutes to many hours in the involved region following the Jacksonian seizure-called Todd's paralysis.
3. *Epilepsia partialis continua:* Rarely the Jacksonian seizure may continue for hours or days-called Epilepsia partialis continua. It is often quite refractory to medical therapy.

Partial sensory seizures:

Causing paraesthesia or tingling or electric sensations in the contralateral face and limbs. These seizures arise from sensory cortex.

Partial psychic seizures

There may be sensation of falling or vertigo. There may be sensation of unusual odors or sounds.

Partial visual seizures

Causing simple visual hallucinations such as ball of light, light flashes and visual hallucination of faces or scenes. There may be illusion that objects are growing *smaller (micropsia) or larger (macropsia).*

Complex partial seizures

Complex partial seizures usually arise from temporal lobe and less frequently from frontal lobe.

Psychomotor (Temporal lobe) Seizure

These complex partial seizures are associated with altered consciousness without the patient collapsing to the ground. The patients stop what he or she is doing and stares blankly, often making rhythmic smacking movements of lips or picking at their cloths. After a few minutes patient gains consciousness but may be drowsy.

Immediately before such an attack the patient may report alteration of mood, memory or perception such as undue familiarity (déjà vu) or unreality (jamais vu). There may be hallucination of sound, smell, taste, vision, fear, sexual arousal, visceral sensations (nausea, epigastric discomfort).

Secondary generalized seizures

Generalized epilepsy may arise from spread of partial seizures due to structural disease or may be secondary to drugs or metabolic disorders. Epilepsy presenting in adult life is almost always secondary generalized, even if there is no clear history of a partial seizure before the onset of a major attack.

GENERALIZED SEIZURES

Generalized seizures start by activation of groups of neurons in large areas of both hemispheres simultaneously. Following are the types of generalized seizures:

Typical absence seizures (petit mal)

This type of generalized epilepsy is almost invariably a disorder of childhood. During an attack the child stops activity, stares, may blink or rolls up the eye and fails to respond to commands. The attack lasts for a few seconds.

Atypical absence seizure

There may be more marked changes in tone, or attacks may have a more gradual onset and termination as compared to in typical absence.

Myoclonic seizures

It consists of single or multiple myoclonic jerks involving one part of the body or the entire body.

Atonic seizures

Atonic seizures are characterized by sudden loss of postural muscle tone lasting 1-2 seconds. Consciousness is briefly impaired.

Tonic clonic seizures

These seizures start with aura, then there is tonic phase followed by clonic (jerky) phase discussed as following:

FACTORS WHICH MAY TRIGGER SEIZURES

- Sleep deprivation
- Emotional stress
- Physical and mental exhaustion
- Infections, pyrexia
- Drug or alcohol ingestion, or withdrawal
- Flickering light, visual patterns, proximally to television screens.
- Uncommon triggers
  Loud noise
  Hot baths
  Music
  Reading

PHASES OF A TONIC-CLONIC SEIZURE

Prodromal phase
Hours or days before attack, unease, irritability.

Aura
These are specific feelings and usually patient anticipates that seiuzure will occur. These feelings may be olfactory hallucination, epigastric discomfort, déjà vu, jerking of one limb.

Tonic phase
Rapid discharging of motor cortex cells causes tonic contractions of muscles; arms flexed and adducted, legs extended; respiratory muscle spasm causes cry as air expelled; cyanosis, loss of consciousness.
This phase lasts 10-30 seconds.

Clonic phase
Less rapid, gradually slowing discharge of cortical cells causes violent jerking of face and limbs, tongue biting and incontinence.
This phase lasts 1-5 min.

Post-ictal phase
Deep unconsciousness, flaccid limbs and jaw, loss of corneal reflexes, extensor plantar responses. Last a few minutes to several hours. Headache, confusion, aching muscles and sometimes automatic behavior, occasional violence.

DIFFERENTIAL DIAGNOSIS OF SEIZURE

D/D of partial seizures

1. Transient Ischemic Attack (TIA)
These attacks are distinguished from seizures by their longer duration and specific symptoms e.g. weakness or numbers. Convulsive jerking characterizes seizures.

2. Panic attacks.
Due to psychopathologic disturbances.

D/D of generalized seizures (episodic loss of consciousness)

1. Syncope
Loss of consciousness for short period (syncope) usually occurs in relation to position change, emotional stress, pain and usually preceded by pallor, sweating and nausea. There is no postictal headache or confusion.

2. Cardiac dysrhythmias

Cerebral hypotension due to disturbance of cardiac rhythm should be suspected in known cardiac or vascular disease or in older patients who present with episodic loss of consciousness

3. Pseudo-seizures

The term pseudo-seizure is used to denote:

- Hysterical conversion reactions
- Attacks due to malingering when these stimulate epileptic seizures.

A number of patients admitted in medical wards for true seizures prove to be having pseudo-seizures. These are characterized by an asynchronous thrashing of the limbs, which increase if restraints are imposed. There is no postictal stage. EEG is normal. Serum prolactin that increases after 15-30 min of true tonic – clonic seizure is unchanged in pseudoseizure.

DIAGNOSIS

History

The most important tool in the diagnosis is to determine whether the event was truly a seizure. During taking history questions should be related to symptoms before, during and after seizure in order to discriminate seizure from other similar conditions given in D/D. History from witness is very important as the patient may be unaware of ictal and postictal phases. Ask about tongue biting, stool or urinary incontinence or injury during alleged seizure.

History should be focused on identifying predisposing factors such as history of febrile seizures, auras, family history of seizures, prior head trauma, stroke, tumor or vascular malformation.

Identify the precipitating factors such as sleep deprivation, systemic diseases, electrolytes or metabolic derangements, acute infection, drugs that reduce the seizure threshold or drug or alcohol withdrawal.

Examination

Examination for predisposing or precipitating factors, injuries getting during seizure. Assessment of mental status, language and abstract thinking.

DIAGNOSING EPILEPSY

- **Take a detailed history from the patient**
- **Interview an eye-witness who has observed attack.**

Specific questions

- **Events leading up to attack**
- **Sleep deprivation, drugs, alcohol, near TV screen.**
- **Time of day or night**
- **Symptoms of aura, duration**
- **Abnormal movements**
- **Limb stiffening, jerking, automatisms**
- **Salivation, cyanosis**
- **Tongue biting, incontinence**
- **Post-ictal symptoms**
- **Limb pains, headache, drowsiness.**

Examination

- **Auscultation of neck and eyes for bruits**
- **Pulse, blood pressure, heart auscultation**
- **Head for evidence of trauma**
- **Skin for lesions of neurofibromatosis**
- **Visual fields, optic fundi**

INVESTIGATIONS

Investigations to rule out metabolic or infectious causes of seizures.

- Blood CP- to look for leukoctosis
- Serum urea, creatinine, electrolytes
- Random blood sugar
- Serum calcium and magnesium
- Liver function tests (LFTs)
- Screen for toxins in blood and urine if toxicity is suspected.
- Lumber puncture – if meningitis or encephalitis is suspected.

Electroencephalography (EEG)

The EEG may help establish and characterize the type of epilepsy. Determination of type is important for determining the most appropriate anticonvulsant drug with which to start treatment.

If the patient is having frequent seizures, such as a child with absence seizures, the EEG may confirm the presence of seizures (by demonstrating spikes or sharp waves) even in inter-ictal period.

In patients with infrequent seizures, the EEG may reveal potentially abnormal activity in between two attacks that when combined with clinical or radiologic data, aids in establishing the diagnosis. However EEG may be normal in inter-ictal period and therefore normal EEG does not rule out epilepsy. Ideally EEG should be performed after sleep deprivation to increase the potential diagnostic yield of the study. EEG in epilepsy shows spikes or spike and wave pattern.

CT or MRI Scan

CT or MRI brain scanning does not help establish a diagnosis of epilepsy but is often useful in defining or excluding structural cause for seizures e.g. tumors, infections. Generalized seizures are often idiopathic but the partial seizures have the highest incidence of detectable cortical lesion. Therefore partial seizures need more intensive investigations, especially require if they arise for the first time in adult life. MRI is superior to CT in detecting cerebral lesions associated with epilepsy. However if CNS infection or mass is suspected CT should be done in emergency if MRI is not immediately available.

As a general rule the CT scan should be performed if:

- Epilepsy starts after the age of 20 years (because of the possibility of an underlying neoplasm). A chest x-ray should also be obtained in such patients, since the lungs are a common site for primary or secondary neoplasm).
- Partial (focal) seizures
- Control of seizures is difficult

CT Scan is not required if a confident diagnosis of primary generalized epilepsy can be made clinically.

PET & SPECT

Position emission tomography (PET) and single photon emission computed tomography (SPECT) are also used to evaluate certain patients of seizures who do not respond to medical therapy.

INVESTIGATIONS IN EPILEPSY

- Full blood count, ESR
- Blood urea, electrolytes, calcium, glucose
- Liver function tests
- Serological tests for syphilis
- HIV serology in high risk groups
- Chest and skull radiographs
- Electrocardiogram (ECG)
- Routine EEG
- Sedated sleep EEG
- 24-hour ambulatory EEG/ECG
- Video / EEG monitoring
- EEG with special electrodes (foramen ovale, subdural).
- Computerized tomography (CT)
- Magnetic resonance imaging)

MANAGEMENT

Immediate care of seizures:

Little can be done for a person having a major seizure. Some simple guidelines are listed as following:

First aid (by relatives and witnesses)

- Move person away from danger (fire, water, machinery, furniture)
- After convulsions cease, turn into 'recovery' position (semi prone).
- Ensure airway is clear
- Do not insert anything in mouth (tongue-biting occurs at seizure onset and cannot be prevented by observers)
- If convulsions continue for more than 5 minutes or recur without person regaining consciousness, summon urgent medical attention.
- Person may be drowsy and confused for some 30-60 minutes and should not be left alone until fully recovered.

Immediate medical care

- Ensure airway is clear
- Give oxygen to offset cerebral hypoxia
- Give intravenous anticonvulsant (e.g. diazepam 10 mg) ONLY if convulsions are continuous or repeated (if so, manage as for status epilepticus).
- Take blood for anticonvulsant levels (if known epileptic)

Avoidance of precipitating factors

Precipitating factors such as sleep deprivation should be avoided.

Treatment of underlying conditions

If the underlying cause is correctable promptly, anti -epileptic drug therapy is unnecessary. However if the underlying cause cannot be corrected promptly and the patient is at risk of having further seizures then give anticonvulsant therapy.

Anticonvulsant drug therapy

When to initiate antiepileptic drug therapy

Traditionally, a single seizure has been regarded as an indication for investigation and assessment, but not for drug treatment unless a second attack follows closely or there is an identified lesion such as brain tumor, infection or trauma, in which there is strong evidence that the lesion is epileptogenic. Drug treatment should certainly be considered after two seizures.

Selection of antiepileptic drugs

The drug with which treatment is best initiated depends upon the type of seizures to be treated.

The dose of the drug is gradually increased until seizures are controlled or side effects prevent further increases. If seizures continue despite treatment at the maximal tolerance dose, a second drug is added and the dose increased depending on tolerance. If there is no improvement, a third drug can be added while the first two are maintained.

Monitoring for side effects

Almost all of the commonly used anti-epileptic drugs cause dose- related side effects such as sedation, ataxia, and diplopia. They also cause idiosyncratic toxicity such as rash, bone marrow suppression or hepatic toxicity, therefore baseline blood count and LFTs should be done.

Measuring plasma anticonvulsant drug level

Plasma level monitoring of the anti-epileptic drugs should be done particularly for phenyton (Dilantin) because of marked variation in dose requirement between individuals. The measurement of plasma levels of carbamazepine (Tegrel) and the barbiturates are helpful but not essential.

Withdrawal of anticonvulsant therapy

After a period of complete control of seizures withdrawal of medication may be considered usually 2-3 years seizure-free period is required before considering withdrawal. Dose reduction should be gradual over a period of 2-3 months. Recurrences if occur mostly develop in first 3 months after discontinuing therapy.

GUIDELINES FOR ANTICONVULSANT THERAPY

- Start with one first-line drug.
- Start with low dose; gradually increase to effective control of seizures or side-effects (use drug levels if appropriate)
- Check compliance (use minimum division of doses)
- If first drug fails (seizures continue or side-effects), start second-line drug whilst gradually withdrawing first
- Try three agents singly before using combinations (beware interactions).
- Do not use more than two drugs in combination
- If above fails, consider whether occult structural or metabolic lesion present.

EPILEPSY: OUTCOME AFTER 20 YEARS

- 50% seizure-free, without drugs, for last 5 years
- 20% seizure-free for last 5 years but continue to take medication.
- 30% seizures continue in spite of anti-epileptic therapy.

Epilepsy, pregnancy and oral contraception

Hepatic enzyme induction caused by carbamazipine, phenytoin and barbiturates accelerates metabolism of the oral contraceptives causing contraceptive failure; therefore alternative method of contraception should be used.

Epilepsy may worsen during pregnancy particularly in third trimester, therefore plasma levels of anti epileptic drugs should be performed more frequently.

All anti-epileptic drugs are teratogenic causing congenital defects, therefore minimum effective

dose should be used, but these drugs cannot be stopped as the seizure is more harmful than the chances of congenital defects. Folic acid 5mg daily taken 2 months before conception may reduce the risk of some fetal abnormalities.

CHOICE OF ANTI- EPILEPTIC DRUGS		
Epilepsy type	First- line	Second -line
Partial or secondary generalized tonic clonic	Carbamazepine	Lamotrigine Sodium valporate Topiramate Tiagabine Gabapentin
Primary generalized tonic - clonic	Sodium valporate	Lamotrigine Topiramate Carbamazepine
Myoclonic	Sodium valporate	Clonazepam
Absence	Ethosuximide	Sodium valporate

New Anticonvulsant drugs

Following new drugs are approved for partial (focal) seizures with or without secondary generalized tonic-clonic seizures. These drugs are licensed for "add on therapy" when partial seizures do not respond to carbamazipine or valporate.

- Lamotrigine (Lamictal)
- Gabapantin
- Febamate
- Topiramate (Topamax)
- Primidone
- Vigabatrin

STATUS EPILEPTICS

This is a medical emergency and life threatening condition when the seizure is prolonged lasting 15-30 minutes or there are repetitive seizures without recovery in between. Patient does not regain awareness between attacks.

Status epilepticus is an emergency, since cardiorespiratory dysfunction, hypertherma, and metabolic derangements can develop as a consequence of prolonged seizures, and these can lead to irreversible neuronal injury after approximately 2 hours.

Precipitating factors

- Abrupt withdrawal of anticonvulsant drugs
- Cerebral hemorrhage
- More common with epileptic focus in frontal lobe.
- Metabolic disturbance
- Drug toxicity
- CNS infection, CNS tumor
- Head trauma
- Refractory epilepsy

Management of status epilepticus

- Secure i.v. access
- Administer oxygen, monitor ECG, BP, respiration.
- Draw blood for glucose and electrolytes and save for future analysis of drug screen, anticonvulsant levels.
- Give thiamine in alcoholics or nutrition poor patient.
- Give diazepam 10 mg i.v. – repeat once only after 15 min; or lorazepam 4mg i.v.
- Give the anticonvulsant drug that patient is already taking.
- If seizures continue, consider i.v. phenytoin 15mg/kg diluted to 10mg/ml in normal saline given through large vein at a rate less than 50 mg/min. (phenytoin sodium injection is available by the name of Dilantin and 5ml ampule contains 250mg). Fosphenytoin is a pro-drug of phenytoin and can be given faster than phenytoin.
- If seizures continue, give Phenobarbital 10mg/kg diluted 1 in 10 for injection and give at rate of < 100mg/min.
- If sezures continue, give thiopentone anesthesia with assisted ventilation.
- Investigate the cause.

Strategy of management of status epilepticus

Diazepam 10mg IV

↓

Diazepam 10mg IV after 15 min

↓

Phenytoin 20 mg/kg IV at @ 50mg/min

↓

Phenytoin 5-10 mg/kg IV at @ 50mg/min

↓

Phenobarbital 20mg/kg at @ 50-100 mg/min

↓

Phenobarbital 5-10mg/kg at @ 50-100 mg/min

↓

Barbiturate or benzodiazepine anesthesia

Anticonvulsant drugs

	Seizure type	Dose range (mg/day)	Doses per day	Therapeutic range (µmol/l)	Dose-related side-effects	Idiosyncratic side-effects	Long-term side-effects	Interactions
Carbamazepine	Partial secondary GTCS	200–2000	2–3	30–50	Drowsiness, ataxia, nystagmus, diplopia, hyponatraemia	Rashes, thrombocytopenia, other blood dyscrasias	None	Other AEDs, warfarin, CCP, steroids, antimalarials, cimetidine
Clobazam	Partial (adjunctive)	20–30	1	Not applicable	Sedation, irritability		Anticonvulsant effect wears off after a few weeks	Other AEDs
Clonazepam	Partial (adjunctive), myoclonus	1–8	2	Not applicable	Sedation, irritability	Blood dyscrasias	Anticonvulsant effect wears off after a few weeks	Other AEDs
Ethosuximide	Childhood absence	500–1500	2	200–700	Dizziness, insomnia, ataxia	Rashes, blood dyscrasias		Other AEDs, antidepressants
Gabapentin	Partial	300–2400	3	Not applicable	Drowsiness, ataxia		Not yet known	Antacids
Lamotrigine	Partial secondary GTCS	25–500	1–2	Not applicable	Drowsiness, ataxia, diplopia, confusion	Rashes, blood dyscrasias	Not yet known	Carbamazepine, valproate
Phenobarbitone	Partial secondary GTCS	60–180	1	50–150	Drowsiness, ataxia, nystagmus, diplopia	Rashes, depression (adults), excitement (children), megaloblastic anaemia, SLE	Folate deficiency, osteomalacia, neuropathy	Other AEDs, anticoagulants, calcium channel blockers, digoxin, steroids, CCF theophylline, thyroxine, antidepressants, antimalarials
Phenytoin	Partial secondary GTCS	150–350	1	40–80	Drowsiness, ataxia, nystagmus, diplopia, tremor, dystonia, asterixis	Rashes, blood dyscrasias, liver damage, SLE	Gum hypertrophy, facial dysmorphism, hirsutism, folate deficiency, osteomalacia, neuropathy	Other AEDs, warfarin, amiodarone and other anti-arrhythmics, antimalarials, steroids, CCP, cimetidine, oral hypoglycaemics, theophylline, thyroxine
Primidone	Partial secondary GTCS	250–1000	1–2	50–150*	Drowsiness, ataxia, nystagmus, diplopia	Rashes, depression (adults), excitement (children), megaloblastic anaemia, SLE	As for phenobarbitone*	As for phenobarbitone*
Sodium valproate	Primary and secondary GTCS, absences, myoclonus	400–2500	1–2	Not applicable	Drowsiness, nausea, ataxia, nystagmus, diplopia, tremor	Alopecia, rashes, blood dyscrasias, liver damage, pancreatitis	Weight gain	Other AEDs, anticoagulants, antimalarials, cimetidine
Topiramate	Partial secondary GTCS	200–600	1–2	Not applicable	Drowsiness, nausea, ataxia, confusion	Nephrolithiasis, depression, taste alteration, diarrhoea, weight loss	Not yet known	Other AEDs, CCP
Vigabatrin	Partial secondary GTCS, infantile spasms	2000–6000	1–2	Not applicable	Drowsiness, nausea, ataxia, confusion	Aggression, alopecia, skin rash, increase in seizures, retinal atrophy	Not yet known	

* Primidone is converted in the liver to phenobarbitone. (GTCS = generalised tonic clonic seizures; AEDs = anti-epileptic drugs; CCP = combined contraceptive pill; SLE = systemic lupus erythematosus; CCF = congestive cardiac failure)

STROKE

Stroke is a focal neurological deficit due to a vascular lesion. It is usually of rapid onset and by definition lasts longer than 24 hours if the patient survives. It presents as weakness, either permanent or transient, of limbs on one side, often with loss or disturbance of speech.

Cerebrovascular diseases (the diseases of cerebral blood vessels) may present as:

- An acute focal stroke due to infarction or hemorrhage OR
- As a decline in intellectual function (dementia) due to gradual cerebral ischemia.

INCIDENCE

- Age: usually above 40 years
- Sex: Male to female ratio 1.5: 1
- Stroke due to cerebral infarction 80-85%
- Stroke due to cerebral hemorrhage 15-20%

RISK FACTORS

Non- modifiable

- Age
- Gender (M> F)
- Heredity
- Previous vascular event such as MI, stroke or peripheral embolism.

Modifiable

- Hypertension
- Cigarette smoking
- Diabetes mellitus
- Hyperlipidemia
- Heart failure
- Atrial fibrillation
- Myocardial infarction
- High alcohol intake
- Positive family history
- Oral contraceptives
- Polycythemia

PATHOPHYSIOLOGY

Stroke may be divided into two groups according to the mechanism of occurrence into cerebral infarction (ischemic stroke) and intracerebral hemorrhage (hemorrhagic stroke).

Cerebral infarction (Ischemic stroke)

Occlusion of a major artery leads to decreased blood flow to the brain resulting in ischemic injury to the brain called cerebral infarction. Occlusion may be due to:

- *Thrombosis:*
  Thrombosis at the site of atherosclerosis in intracranial or extracranial arteries (e.g. internal carotid artery at its origin & vertebrobasilar artery) leads to vascular occlusion and brain ischemia and infarction.

- *Embolism*
  Embolism of a thrombus from extra cranial artery or heart causes obstruction of cerebral arteries leading to ischemia and infarction.

Once deprived of blood supply, cerebral tissue undergoes infarction within a few minutes. The damaged neurons and glia become edematous after some hours, the resultant cerebral edema causes more damage by further impairing cerebral blood flow.

Cerebral hemorrhage (Hemorrhagic stroke)

It may be due to primary intracerebral hemorrhage or subarachnoid hemorrhage:

Primary intracerebral hemorrhage

Primary intracerebral hemorrhage occurs due to rupture of small perforating arteries or arterioles weakened by hypertension or atheromatous degeneration, producing microaneurysm.

Intracerebral hemorrhage tends to occur at three distinct sites: Cerebellum, pons, internal capsule. Cerebral hemorrhage can be fatal if secondary compression of the brain stem occurs.

Subarachnoid hemorrhage

Subarachnoid hemorrhage develops from rupture of an aneurysm at the circle of Willis.

CAUSES OF ISCHEMIC STROKE

Thrombosis

1. *Extracranial atherosclerosis*
   Most commonly involving the origins of the common carotid artery, origins of the internal carotid arteries, origins of vertebral arteries. Atherosclerotic plaque itself can cause arterial stenosis or there is formation of thrombus on ulcerated surface of plaque occluding the vascular lumen.

2. *Intracranial atherosclerosis*

3. *Vasculitis*
   Temporal arteritis, polyarteritis nodosa, bacterial or granulomatous arteritis due to meningitis, tuberculosis or fungi.

4. *Blood disorders*
   Polycythemia, thrombocytosis, DIC.

5. *Arterial dissection*
   Arterial dissection of carotid, vertebral or intracranial arteries.

6. *Miscellaneous*
   Cocaine, amphetamine

Embolism

Cardiac source

- Atrial fibrillation
- Myocardial infarction (esp. anterior wall MI causing left ventricular thrombus formation)
- Cardiomyopathies
- Mitral stenosis, mitral valve prolapse
- Infective endocarditis
- Prosthetic valves
- Atrial myxoma

Atheroembolic arterial source

- Ulceration of atheromatous plaque may cause dislodgment of necrotic materials that serve as emboli.

- Hypercoaguable states causing thrombosis and embolism such as cancer, oral contraceptives, deficiency of anticoagulant factors such as Factor C, factor S and anti-thrombin III, presence of antiphospholipid antibodies.

CAUSES OF HEMORRHAGIC STROKE

- Hypertension
- Ruptured cerebral aneurysm
- Ruptured AV malformation
- Systemic bleeding disorder and anticoagulant therapy
- Anticoagulant therapy
- Hemorrhagic infarction
- Cocaine or amphetamine abuse
- Trauma
- Amyloid angiopathy (age related)

VASCULAR ANATOMY OF BRAIN

Brain is supplied by four major vessels, the paired internal carotids and vertebral arteries.

Each **internal carotid artery** gives retinal artery and then enters the skull, divides into anterior and middle cerebral arteries, which are responsible for anterior intracranial circulation.

Vertebral arteries originate from subclavian arteries and inside the skull each vertebral artery gives posterior cerebellar artery and then fuses with each other to form basilar artery that divides into two posterior cerebral arteries.

BLOOD SUPPLY OF BRAIN
Anterior cerebral artery
Anterior cerebral artery supplies medial surface of the cerebral hemisphere as far back as the parietal lobe. This area includes: • Portions of motor and sensory cortex related to contralateral leg and bladder • Inhibitory or micturition center.
Middle cerebral artery
Middle cerebral artery supplies lateral surface of cerebral hemisphere that includes • Motor and sensory cortex representation of face, hand, arm. • Expressive (Broca's) and receptive (Wernick's) language areas • Visual cortex • Basal ganglia
Vertebrobasilar artery
Vertebrobasilar artery: the vertebral artery, basal artery and posterior cerebral arteries supply: • Brain stem • Thalamus • Posteriomedial aspects of the cerebral hemispheres.

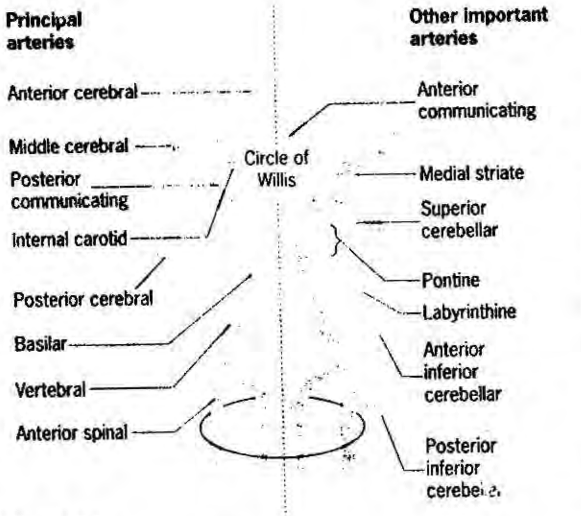


Fig 18.17
Arteries supplying the brain

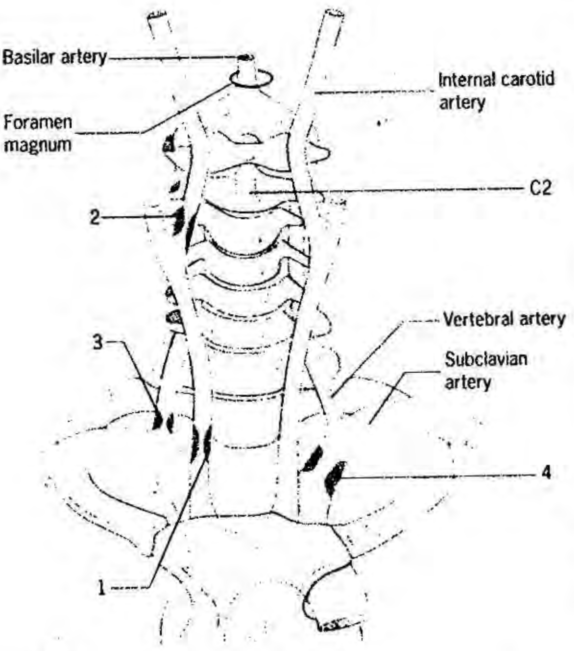


Fig 18.19
Principal sites of atheromatous stenoses in extracerebral arteries

CLINICAL CLASSIFICATION OF STROKE

1. Transient ischemic attacks (TIAs)
When the symptoms of stroke are lasting less than 24 hours, it is called TIA. The symptoms usually reach their peak in seconds and last for minutes or hours (but by definition less than 24 hours). TIAs have tendency to recur, and to herald stroke.

2. Evolving stroke
When the symptoms of stroke worsen gradually over a period of hours or days, it is called evolving stroke. It is thought that thrombus extends from its site of origin and progressively obliterates collateral branches, therefore leading to stepwise increase in focal neurological deficit.

3. Complete stroke
When stroke evolves rapidly over a few minutes and reaches to maximum disability within an hour or two, and the symptoms lasting longer than 24 hours, it is called complete stroke.

4. Minor stroke
When the patients recover without a significant deficit, usually within one week.

TRANSIENT ISCHEMIC ATTACKS

Transient ischemic attacks are caused by the passage of emboli (90%) or, less commonly, by a fall in cerebral perfusion (e.g. due to a cardiac dysrhythmia, postural hypotension or reduced blood flow through atheromatous vertebral arteries).

The principal source of emboli is atheromatous plaque within the carotid or vertebral arteries or from mural thrombus formed on diseased heart muscle. Less common causes of TIAs include the conditions given under the causes of ischemic stroke.

There is complete functional recovery from TIA. Focal neurological deficits depend on the artery involved.

Clinical features

TIAs cause sudden loss of function in one region of the brain. Symptoms reach their peak in seconds and last for minutes or hours (but by definition less than 24 h). Consciousness is usually preserved.

Features of TIA when ischemia involves internal carotid territory.

- *Weakness* and heaviness of the contralateral arm, leg or face singly or in combination.
- *Numbness* or paraesthesias may also occur either as the sole manifestation or in combination with the motor deficit.
- *Aphasia* may be present
- *Visual loss* in one eye due to involvement of ophthalmic branch of internal carotid (called amaurosis fugax).

Features of TIA when ischemia involves vertebrobasilar territory

Vertigo, ataxia, diplopia, dysarthria, dimness or blurring of vision, perioral numbness, weakness or sensory loss on one, both or alternating sides of the body. Drop attacks due to bilateral leg weakness may occur.

Examination of patient with TIA

On examination there may be flaccid weakness, sensory loss, hyperreflexia, extensor planter response on the affected side. Carotid bruit may be present.

Source of embolus may be evident such as:

- Valvular heart disease or endocarditis
- Recent myocardial infarction
- Atrial fibrillation

Associated disease may be evident such as:

- Atheroma
- Hypertension
- Postural hypotension
- Bradycardia or low cardiac output
- Diabetes mellitus

Features of Transient Ischemic Attacks

Anterior circulation (carotid system)	Posterior circulation vertebrobasilar system
Hemiparesis Hemisensory loss Aphasia Amaurosis fugax Hemianopic- visual loss	Diplopia, vertigo, vomiting Choking and dysarthria Ataxia Hemisensory loss Transient global amnesia Loss of consciousness (rare)

Amaurosis fugax: Transient monocular blindness.
Transient global amnesia: Episodes of amnesia with confusion lasting for several hours caused by ischemia posterior circulation.

Differential diagnosis of TIA

(D/D of transient loss of cerebral function)

- *Focal epilepsy:* accompanied by jerking of the limbs, but not in TIA
- *Migraine*: Headache & visual disturbance but not in TIA.

Investigations

Investigations to identify predisposing factors:

- Blood CP
- FBS,
- Serum cholesterol,
- ECG,
- X-ray chest,
- Echocardiography if cardiac source is likely.
- Blood culture if endocarditis is suspected.
- Carotid doppler

Treatment

Medical treatment

Medical treatment is aimed at preventing further attacks and stroke.

Embolization from heart

- Anticoagulants such as heparin followed by warfarin should be given in case of embolism from heart provided no contraindication.
- If anticoagulants are contraindicated platelet aggregation inhibitor such as aspirin is used in a dose of 300 mg per day.

Embolization from extracranial or intracranial cerebrovascular circulation

- Aspirin 300mg daily.
- Ticlidipine (Ticlid 250 mg) twice daily is used if the patient is intolerant of aspirin. Monitor for neutropenia.Treatment of predisposing factors is essential.

Surgical treatment

Carotid endarterectomy reduces the risk of stroke and is indicated when the carotid artery is severely stenosed (70-99% in luminal diameter on angiography). Now symptomatic patients with 50-69% stenosis are also considered for endarterectomy. Asymptomatic patient with stenosis > 80% should also be considered for endarterectomy because it predisposes to stroke.

Surgery is not indicated for mild stenosis and is managed medically. Similarly patients with vertebrobasilar ischemia are also treated medically.

Subcutaneous angioplasty
Patients who are not good candidates for surgery because of medical comorbidities can be considered for angioplasty and stenting. Carotid stenting is associated with 5-18% risk of periprocedural stroke or TIA.

Prognosis:

Five years after the TIA:

- One out of six patient will have suffered a stroke
- One out of four patients will have died usually from heart disease or stroke.

EVOLVING STROKE

In the type of stroke the symptoms worsen gradually or in a stepwise fashion over a period of hours or days. It is caused by slow occlusion of major cerebral vessel such as the internal carotid or the middle cerebral artery.

This clinical picture can be due to cerebral tumor or subdural hematoma (D/D). It is important to recognize evolving stroke because anticoagulation can prevent evolving stroke into complete stroke.

FEATURES SUGGESTING EMBOLIC STROKE

- Sudden neurological deficit with no warning and maximal at onset i.e. not presenting as evolving stroke.
- Seizures at the onset of stroke are more common with embolus.
- Multiple cerebral arteries may be involved in case of cardiac emboli.
- Presence of predisposing factors such as atrial fibrillation, valvular heart disease, endocarditis, anterior wall MI.

COMPLETE STROKE

CEREBRAL INFARCTION

CLINICAL FEATURES

The clinical features depend on the site and extent of the infarct.

Obstruction of carotid circulation

Middle cerebral artery obstruction
Middle cerebral artery is the most commonly involved artery. The most common stroke is the hemiplegia caused by infarction of internal capsule following occlusion of lentriculostriate branch of middle cerebral artery. Its occlusion leads to the following deficits on the opposite side of lesion:

- Hemiplegia (face and arm > leg)
- Hemisensory loss
- Homonymous hemianopia (bilaterally symmetric loss of vision in half of the visual fields).
- Aphasia (loss of speech) if the dominant hemisphere is involved. Dominant hemisphere is left in right-handed and 70% of left-handed persons.
- Occlusion of internal carotid artery presents with the similar features like that of middle cerebral artery.

Anterior cerebral artery obstruction
Anterior cerebral artery stroke is uncommon because emboli from the extracranial arteries or the heart are more apt to enter the large caliber middle cerebral artery which receives the bulk of cerebral blood flow. Secondly collateral from opposite side in the form of anterior communicating artery prevents ischemia. When there is occlusion of anterior cerebral artery distal to the junction of anterior communicating artery, stroke develops with the following features:

- Hamiparesis and cortical sensory loss (leg > arm and face)
- Urinary incontinence due to failure to inhibit the reflex bladder contraction.

Obstruction of vertebrabasilar circulation

Posterior cerebral

- Hemianopia, cortical blindness
- Amnesia
- Thalamic pain

Obstruction of cerebellar and basilar arteries produce symptoms and signs of brainstem dysfunction such as ataxia, diplopia, nystagmus, dysarthria, dysphagia, cranial nerve palsy, bilateral sensory symptoms, loss of consciousness

Sensory and motor deficits are crossed i.e. affecting face on one side and limbs on other side of body.

Comparison of symptoms of stroke due to occlusion of anterior (carotid) & posterior (vertebrobasilar) circulation

Symptoms	Carotid %	Vertebro-basilar %
Headache	25	3
Altered consciousness	5	16
Aphasia	20	0
Visual field defects	14	22
Diplopia	0	7
Vertigo	0	48
Dysarthria	3	11
Drop attack	0	16
Hemi or monoparesis	38	12
Hemisensory loss	33	9

Stroke and unconsciousness

In uncomplicated stroke consciousness is not impaired, patient becomes drowsy or comatose when they develop large infarcts or considerable cerebral edema that disturbs the function of the other hemisphere or brainstem. Coma also occurs with bilateral brainstem infarction when this involves the reticular formation.

Note:

In upper motor neuron lesion tone is increased and reflexes are exaggerated however initially the paralyzed limb may be flaccid and reflexes can be depressed despite an extensor planter response (due to spinal shock). After a few days reflexes recover and become exaggerated and tone of muscles is increased on the affected side. Weakness recovers gradually over the course of days, weeks or months. Majority of patients in wards are in initial stages and therefore with decreased tone and diminished reflexes.

Brainstem infarction

Infarction in the brainstem causes complex pattern of dysfunction depending on the site involved:

Lateral medullary syndrome

The most common of the brainstem vascular syndromes, is caused by occlusion of the posterior inferior cerebellar artery. It presents with sudden vomiting, vertigo, dysphagia, ipsilateral Horner's syndrome. On the side opposite the lesion there is loss of pain and temperature.

Coma

Coma develops when bilateral brainstem infarction damages the reticular formation.

Pseudobulbar palsy

Pseudobulbar palsy can be caused by brainstem infarction.

Clinical signs in the lateral medullary syndrome

Ipsilateral	Contralateral
Facial numbness (5th) Diplopia (6th) Nystagmus Ataxia Horner's syndrome Ninth and tenth-nerve lesion	Spinothalamic sensory loss Hemipatesis (mild, unusual)

Other patterns of infarction

Lacunar infarction

These are small infarction < 1.5 cm in the deep white matter of the hemisphere or brain stem and seen on MRI or CT contrast. They are usually due to hypertension-induced lipohyalinosis or arteriosclerosis of small arteries. Minor strokes (e.g. pure motor stroke, pure sensory stroke) develop by single lacunar infarct. Lacunar infarction may be asymptomatic.

Hypertensive encephalopathy

Hypertensive encephalopathy is characterized by accelerated hypertension associated with somnolence, confusion, visual disturbances, nausea and vomiting.

High systemic intravascular pressure causes multifocal cerebral arteriolar vasodilatation and microhemorrhages and ischemia of brain.

(D/D uremia, encephalitis, cerebral venous sinus thrombosis, DIC and bacterial endocarditis).

Urgent treatment with IV sodium nitroprusside or nitrglycerine is required.

Cerebral venous sinus thrombosis

Causes

- Late pregnancy and postpartum state
- Severe dehydration
- Infection spreading from face, sinus, mastoid or brain abscess
- Hypercoagubility due to malignancy, DIC.

Diagnosis and management

It presents with headache, bilateral weakness of the legs and to lesser degree of arms; and seizures. CT scan or MRI shows one or more bilateral hemorrhagic infarctions in parasagittal cerebral area. Early treatment with IV heparin can reduce the morbidity and mortality.

CAUSES AND INVESTIGATIONS OF ACUTE STROKE IN YOUNG PATIENTS

Cause	Investigations
Cardiac embolism Atrial fibrillation, post-myocardial infarction	Echocardiography
Premature atherosclerosis	Serum lipids
Arterial dissection	MRI, angiography
Thrombophilia (hypercoagulation)	Protein S and C deficiency, antithrombin III deficiency
Homocystinuria	Urinary aminoacids, methionine loading test
Anticardiolipin syndrome	Anticardiolipin antibodies
SLE	Antibodies
Vasculitis	ESR, CRP, ANCA
Primary intracerebral hemorrhage AV malformation Bleeding disorder	 Angiography PT, APTT, platelets
Subarachnoid hemorrhage Berry aneurysm AV malformation Carotid dissection	Angiography

GENERAL EXAMINATION OF STROKE PATIENT

Eyes

- Diabetic retinopathy
- Hypertensive retinopathy
- Retinal emboli
- Arcus senilis

CVS

- Blood pressure (hyper or hypotension)
- Pulse (irregular in AF)
- JVP (raised in heart failure)
- Peripheral pulses and carotid bruit
- Heart murmur (as source of embolism)

Respiration

- Respiratory infection
- Pulmonary edema

Abdomen

- Urinary retention

INVESTIGATIONS:

CT Scan

- After stroke CT scan is performed immediately to rule out intracerebral hemorrhage, however infarction may not be visible up to 12 hours or more and lacunar infarcts may not appear at all.
- CT scan (without contrast) demonstrates site of lesion and distinguishes between a hemorrhage and infarction. Infarct appears as an area of low density (more blackish while hemorrhage appears as high density (more whitish) area.
- CT scan is preferable to MRI in the acute stage because it is quicker and because intracranial hemorrhage is not easily detected by MRI within the first 48 hours after a bleeding episode.

Carotid Doppler

If the infarction is in the territory of carotid circulation carotid Doppler is performed to identify the degree of stenosis. Patients with carotid stenosis more than 70% should be considered for endarterectomy if he/she had TIA or stroke in anterior circulation and recovered.

Angiography

Magnetic resonance angiography (MRA) or conventional carotid angiography is required to diagnose surgical accessible arterial stenosis for endarterectomy.

Investigations to identify risk factors

Blood sugar, cholesterol, hemoglobin, ECG, echo, ANA, anti-DNA, protein C, protein S and antithrombin III.

General measures

1. Careful nursing:

- Patient should be nursed with the head in a flat position.
- Patient should be kept in semiprone position in order to avoid falling back of tongue.
- Frequent change of position is necessary to prevent lung congestion and bed sores.

2. Maintenance of airway:
In unconscious patient tongue must be kept forward to clear airway by use of an "airway". Regular suction of secretions by oropharyngeal tube.

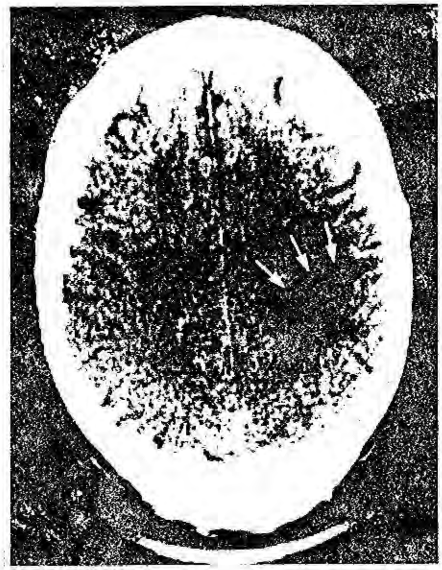
3. Maintenance of fluid balance and nutrition:
In an unconscious patient it can be achieved by passing nasogastric tube (Ryle's tube). In first 24 hours 5% glucose (5% D/W) 2000 ml is adequate, this can be replaced after 24 hours by milk, Complan & other fluid diet. Feeds are given 2-hourly and small in amount to prevent risk of aspiration. Intake output charts should be maintained.

4. Care of skin
Skin should be kept dry and clear. Areas of reddening of skin over heals, ankles, buttocks, shoulders and elbows are indications of impending pressure necrosis (bed-sores) and indicate that the patient is not being turned frequently enough. If bedsores develop, pus culture should be sent, proper daily dressing is performed and antibiotics are prescribed.

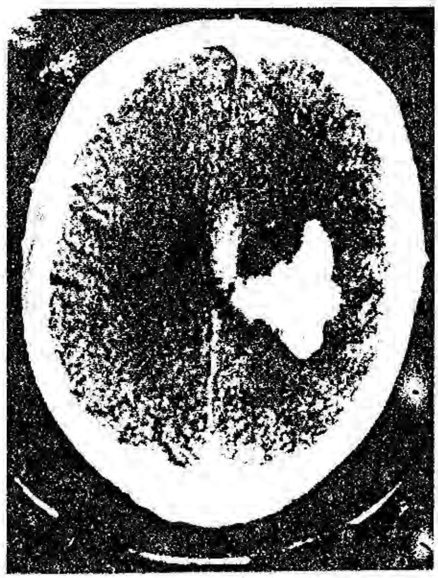
5. Care of bladder and bowel
Bladder catheterization if there is urinary incontinence. Enemas 1-2 time a week if constipation develops.

6. Care of eyes
Antibiotic drops to prevent exposure keratitis in unconscious patient who is unable to close the eyes properly.

7. Physiotherapy
Passive movements should be started from the first day (in infarction but not in hemorrhage) to prevent contractures, to decrease risk of leg vein thrombosis and to promote recovery of muscle strength.



Cerebral infarction (black)



Intracerebral hemorrhage (white)

GENERAL MEASURES

1. Careful nursing
2. Maintenance of airway
3. Maintenance of fluid balance & nutrition
4. Care of skin
5. Care of bladder 7 bowel
6. Care of eyes
7. Physiotherapy

Specific measures for ischemic stroke

Blood pressure control

The blood pressure is usually acutely raised after stroke. This is a compensatory mechanism attempting to maintain cerebral blood flow. Therefore hypotensive agents should not be given at this stage unless there is severe hypertension (220/120 mmHg or above) or there is end-organ damage. Blood pressure returns towards the patient's normal level within 24-48 hours. Attempts to lower the blood pressure of hypertensive patients during the acute phase (i.e. within 2 weeks) of stroke should generally be avoided. However if systolic blood pressure is more than 200 mmHg, it should be lowered with continuous monitoring to 170-200 mmHg and then after 2 weeks the blood pressure should be reduced further to less than 140/90 mmHg for further prevention of stroke.

If treatment is necessary, this should be gentle to avoid a sudden lowering of cerebral pressure, which can exacerbate infarction because perfusion of brain is reduced when pressure is low in the presence of stenosed arteries.
Antiplatelet therapy

Antiplatelet therapy

Platelets aggregation inhibitors inhibit the formation of platelet aggregates that can develop on diseased arteries, form thrombus and occlude the vessel. Aspirin is the most widely used antiplatelet used as prophylactic in TIAs and to prevent expansion of thrombus after stroke. It should be started immediately after hemorrhage is ruled out by CT scan. Dose of aspirin is . 300 mg/day. Ticlodipine may be given instead of aspirin if patient is intolerant to aspirin.

Edema reducing agents

About 5-10% patients of stroke develop symptomatic vasogenic cerebral edema manifesting as altered conscious. Larger the infarct, the more likely edema will be a problem. Management is restriction of free water and administration of intravenous mannitol or steroids.

- Inj. Mannitol 20% 200ml I/V over period of 10-20 minutes.OR
- Inj. Dexamethasone (Decadrone) 4 mg I/V 6 hourly.

Anticoagulants

There is no indication for the use of anticoagulants in acute stroke except:

- If there is clear persisting embolic source e.g. atrial fibrillation.
- Features of stroke evolving over hours or days e.g. patient develops mild aphasia or hemiparesis that progresses into more severe deficits such as complete aphasia or hemiplegia.

Even in both above conditions hemorrhage should be ruled out by CT Scan before anticoagulant is started: Heparin I/V infusion is started 5000 units stat then 1000 units hourly for 2-5 days, during this period patient is monitored for hemorrhagic complications and a decision is made regarding the need of long-term warfarin or antiplatilet therapy.

Thrombolytic therapy

Thrombolytic therapy with tissue plasminogen activator (tPA) shows benefit if given within three hours after onset of ischemic stroke provided CT rule out hemorrhage, however it increases

Internal carotid endarterectomy

It should be considered if patient recovers from stroke, stenosis is more than 70% to prevent further stroke.

COMPLICATIONS OF ACUTE STROKE

Complication	Prevention	Treatment
Chest infection	Nurse in semi-erect position Chest physiotherapy	
Dehydration	Feeding with N/G tube	Rehydration
Hyponatremia	Avoid excess water	Water deprivation
Hypoxemia	Avoid chest complications	Oxygen
Seizures	Maintain cerebral oxygenation Avoid metabolic disturbance	Anticonvulsants
Hyperglycemia	Treat diabetes	Insulin
DVT Pulmonary embolism	S/C heparin	Anticoagulation (but not in hemorrhagic stroke)
Frozen shoulder	Physiotherapy	Physiotherapy Local steroid injection
Bed sores	Frequent change position	Antibiotics Pressure rings
Urinary infection	Avoid catheterization if possible	Antibiotics
Constipation	Appropriate diet	Laxatives

HEMORRHAGIC STROKE

Spontaneous cerebral hemorrhage may occur primarily into the substance of brain (intracerebral) or over its surface (subarachnoid).

INTRACEREBRAL HEMORRHAGE

Spontaneous intracerebral hemorrhage is the cause of about 30% of stroke. It results from rupture of microaneurysms (Charcot-Bouchard aneurysms) that develop typically in patients of hypertension.

Sites of bleeding

Basal ganglia, pons, cerebellum

Clinical features

Intracerebral hemorrhage occurs suddenly when the patient is awake often during activity. It presents with an abrupt onset of severe headache and focal neurologic deficit that typically worsens steadily over 30-90 minutes.

Common Symptoms and Signs of Intracerebral Hemorrhage

Location	Neurologic Signs
Basal ganglia	Contralateral hemiparesis, hemisensory loss, and homonymous hemianopia Aphasia with dominant hemisphere Conjugate deviation of eyes downward or toward the side of the hematoma Obtundation, stupor, or coma
Cerebellum	Vomiting and ataxia Skew deviation of eyes and small pupils Deviation of eyes toward the opposite side Obtundation, late-developing stupor, or coma
Pons	Abrupt onset of coma Pinpoint, reactive pupils Skew deviation of eyes and gaze paresis Decerebration or flaccidity Ataxic respiration

Investigations

CT scan reliably detects acute focal hemorrhages of 1cm or more in diameter. Small pontine hemorrhages may not be identified because of bone artifact that obscures structures in the posterior fossa.

Management

Approximately 75% of patients with a hypertensive intracerebral hemorrhage die. The size and location of the hematoma determine prognosis. Supratenotorial hematomas > 5cm have a poor prognosis and infratentorial hematomas > 3cm are usually fatal.

Surgical evacuation

Evacuation of hematoma usually is not helpful, except in cerebellar hemorrhage. For cerebellar hemorrhage neurosurgeon should be immediately consulted for evacuation.

Medical management

- Mannitol is used to reduce intracranial pressure that raises because of pressure effect of hematoma and due to cerebral edema.
- Blood pressure should be managed but very gently.
- Nursing care as described in management of ischemic stroke.

SUBARACHNOID HEMORRHAGE (SAH)

The term subarachnoid hemorrhage (SAH) describes spontaneous (rather than traumatic) arterial bleeding into the subarachnoid space.
Most of the SAH result from rupture of berry (sacular) aneurysms of one of major cerebral arteries or their branches at the circle of Willis.

SAH is responsible for 8-10% of all strokes.

> **UNDERLYING CAUSES OF SUBARACHNOID HEMORRHAGE**
>
> - Saccular (berry) aneurysms 70%
> - Arteriovenous malformation 10%
> - No lesion found 20%
>
> **Rare associations**
>
> - Bleeding disorders
> - Mycotic aneurysms in endocarditis
> - Acute bacterial meningitis
> - Brain tumors
> - Arteritis e.g. in SLE
> - Coarctation of aorta
> - Marfan's syndrome
> - Ehlers- Danlos syndrome
> - Polycystic kidneys

Clinical features

SAH often occurs during exertion (e.g. straining, sexual intercourse).

Symptoms due to rapidly increasing intracranial pressure with meningeal irritation.

- Headache: sudden, severe radiating to occipital region.
- Vomiting & loss of consciousness following the headache
- Neck stiffness
- Photophobia
- Tonic-clonic seizure sometimes provoked
- Fundoscopy: may show subhyaloid and retinal hemorrhages and sometimes papilloedema

Focal neurological symptoms due to compression of neighboring cranial nerves by blood clot.

- Visual field defects: due to compression of optic nerve
- 3rd, 4th, and 6th nerve involvement
- Hemiparesis

Investigations

CT Scanning:
It is the investigation of choice; it will demonstrate blood in subarachnoid space is about 90% of cases.

Lumbar puncture:
It is performed when SAH is suspected & CT scan fails to show bleeding. Lumber puncture may result in herniation of brain due to raised intracranial pressure, therefore should not be performed routinely, but should be considered when doubt. The CSF becomes yellow (xanthochromic) several hours after SAH.

Management

Mostly patients of SAH are dead or die in a few days. Coma & severe neurological deficits have a poor prognosis. In others, where angiography demonstrates aneurysm, a direct neurosurgical approach to clip the neck of the aneurysm is carried out. Immediate supportive measures are:

- Control of hypertension
- Dexamethasone to reduce cerebral edema.

SUBDURAL HEMORRHAGE

Subdural hemorrhage describes the accumulation of blood in the subdural space following rupture of a vein. It is almost always due to head injury. The interval between injury and symptoms may be days, weeks or months. Headache, confusion and drowsiness are common; hemiparesis or sensory loss may develop. Subdural hemorrhage is common in elderly and alcoholics because they are prone to injuries, even minor.

EXTRADURAL HEMORRHAGE

It results from skull vault fracture which tears a branch of middle meningeal artery. The most characteristic picture is of a head injury with a brief duration of unconsciousness followed by a lucid interval of recovery. The patient then develops a progressive hemiparesis and stupor, and rapid trantenotrial coning, with ipsilateral dilated pupil, followed by bilateral fixed dilated pupils, tetraplegia and death.

CT scan is immediately performed and neurosurgical evacuation of hematoma is performed.

CASE PRESENTATION OF STROKE

HISTORY

Predisposing factors

- Factors for atherosclerosis: hypertension, diabetes, smoking, and hyperlipidemia
- Factors for embolism: ischemic or valvular heart disease, arrhythmias,
- Previous TIAs or stroke.

Onset

- Gradual onset in evolving stroke due to thrombosis
- Sudden onset due to embolism or hemorrhage.

Associated features

- Seizure, headache, altered consciousness.

PHYSICAL EXAMINATION

- *Blood pressure*: may disclose hypertension
- *Pulse:* may show arrhythmia; compare pulses to reveal difference related to atherosclerosis and coarctation of aorta.
- *Examination of neck*: feel for absence of carotid pulse, auscultate for carotid bruit.
- *Cardiovascular examination:* detect source of emboli such as arrhythmia, murmur related to valvular heart disease.
- Palpation of temporal artery for giant cell arteritis.
- *Fundoscopy:* to see the emboli in retinal arteries.

NEUROLOGIC EXAMINATION

Goal of neurologic examination is to detect anatomic site of lesion. It is important because treatment and prognosis is based on anatomic site of lesion, for example we can perform surgery if lesion is in carotid circulation, while in case of vertebrovascular artery lesion and lacunar infarction only medical treatment is offered.

Lesion of stroke may be at one of the following three sites:

- Cerebral cortex: due to wide distribution of motor area in cerebral cortex, there may be monoplegia or incomplete hemiplegia. Patient presents with uncrossed hemiplegia i.e. involvement of face and limbs on the same side.
- Corona radiata and internal capsule: they also present as uncrossed hemiplegia.
- Brainstem: it presents as crossed hemiplegia i.e. hemiplegia affecting the face on one side and limbs on other side of the body.

Cerebral cortex

Frontal lobe lesion presents as:

- Monoplegia or hemiplegia depending on extend of damage.
- Dysphasia (difficulty in speaking) due to involvement of Broca's area in dominant hemisphere.
- Paralysis of head and eye movement to opposite side.
- Change of personality with antisocial behavior
- Incontinence of urine and feces
- Positive grasp reflex (normally it is only positive in infants).

Parietal lobe lesion presents as

- Lesion of either dominant or non-dominant sensory cortex presents with contralateral disturbance of cortical sensations as following.
- Postural sensation and sensation of passive movement are disturbed.
- Loss of accurate localization of light touch (tactile localization)
- Discrimination between two points is lost
- Loss of appreciation of size, shape, texture and weight (astereognosis).
- *Sensory inattention:* when both limbs are touched at the same time patient is only aware of that one contralateral to the normal parietal lobe while when is touched separately patient can recognize the both limb.

Lesion of dominant parietal lobe presents as:

- Inability to distinguish between right and left limbs.
- Finger agnosia: difficulty in distinguishing fingers.
- Acalculia: disturbance of calculation
- Agraphia: disturbance of writing.

Lesion of non-dominant parietal lobe presents as:

- Loss of awareness of opposite limb, patient denies weakness (indifference to illness).
- Difficulty in dressing.
- Constructional apraxia: patient cannot arrange objects in a simple design although he understands it.

Temporal lobe lesion presents as:

- Cortical deafness
- Auditory hallucination
- Olfactory hallucination
- Disturbance of memory
- Complex partial seizures
- Wernick's aphasia when lesion is in dominant hemisphere.

Occipital lobe lesion presents as:

- Cortical blindness
- Visual hallucinations
- Visual illusions e.g. micropsia or macropsia (objects looking smaller or larger respectively).

Lesion in internal capsule

- Complete contralateral hemiplegia as fibers are condensed in a small area.
- Patient is conscious and alert.
- Visual field defect rare.

Lesion in brain stem

- Patient presents with crossed hemiplegia i.e. one or more than one cranial nerves of one side while the hemiplegia of other side of body.
- Lesion of midbrain presents with III nerve palsy, lesion of pons with VI and VII nerve palsy and lesion of medulla presents with IX, X, XI, XII nerve palsy.

DISORDERS OF CRANIAL NERVES

CRANIAL NERVES

No	Nerve	Function
I	Olfactory	Smell
II	Optic	Vision, fields, afferent light reflex
III	Oculomotor	Eyelid elevation, eye elevation, Adduction, depression in Abduction, efferent – to pupil.
IV	Trochlear	Eye intorsion, depression in Aduction
V	Trigeminal	Facial and corneal sensation, muscles of mastication
VI	Abducent	Eye Abduction
VII	Facial	Facial movement, taste fibers
VIII	Vestibular Cochlear	Balance Hearing
IX	Glossopharyngeal	Sensation – soft palate, taste fibers
X	Vagus	Palatal movement, vocal cords, cough.
XI	Accessory	Head turning shoulder shrugging
XII	Hypoglossal	Tongue movement.

I OLFACTORY NERVE

Anosmia: loss of sense of smell (anosmia) occurs with

- Head injury
- Tumors of olfactory groove (meningioma, frontal glioma)
  Nasal obstruction, and after upper respiratory viral infection as in common cold.

II OPTIC NERVE

Examination of visual system comprises

1. Visual acuity
2. Color vision
3. Field of vision
4. Fundoscopy
5. Pupillary reflexes

1. Visual acuity

Near vision can be tested by asking the patient to read some standard charts or read a book or newspaper. Far vision is tested with Snellen chart that has letters of different sizes arranged in lines. The normal acuity is 6/6, i.e. patient can read second line of Snellen chart from 6 meter distance.

Defects in visual acuity may be due to:

- *Ocular causes:* glaucoma, macular degeneration, cataract, and retinal detachment or diabetes vascular disease.
- *Central lesions of the visual pathway:* lesion of optic nerve, optic chiasma, optic tract, optic radiation or visual cortex in occipital lobe.

2. Color vision

Color vision is checked by Ishihara chart that has different colors. Defects of color vision may be congenital due to X-linked disease or acquired due to diseases of macula or optic nerve. Stroke of bilateral occipital lobes may give rise to color blindness.

3. Field of vision

Field of vision is checked by perimetry, however on bedside confrontation method is used to assess the field of vision. In this method examiner compares his on field of vision with that of patient.

Defects in field of vision

Vision can be impaired by damage to the visual system anywhere from the retina to the visual cortex (occipital lobe) and discussed under the following headings:

1. Retinal lesions
2. Optice nerve lesions
3. Optic chiasma lesions
4. Optic tract and optic radiation lesions
5. Occipital cortex lesions

1. Retinal lesion

Retinal lesions may produce scotomata (small areas of visual loss). Common causes are diabetic retinopathy, glaucoma and retinitis pigmentosa.

2. Optic nerve lesion

Unilateral visual loss is the hallmark of optic nerve lesion. A complete lesion of the optic nerve produces total unilateral visual loss with loss of papillary light reflex.

CAUSES OF AN OPTIC NERVE LESION

- Optic and retrobulbar neuritis
- Optic nerve compression (e.g. tumour or aneurysm)
- Toxic optic neuropathy (e.g. tobacco, ethambutol, methyl alcohol, quinine)
- Syphilis
- Ischaemic optic neuropathy (e.g. giant cell arteritis)
- Hereditary optic neuropathies.
- Severe anemia
- Vitamin B_{12} deficiency
- Trauma
- Infective spread of paranasal sinus infection or orbital cellulites)
- Papilloedema and its causes
- Bone disease affecting optic canal (e.g. Paget's)

The principal pathological appearances of the visible part of optic nerve (optic disc) seen on fundoscopy due to optic nerve lesion are:

- Disc swelling (papilloedema)
- Pallor (optic atrophy)

Papilloedema

Papilloedema means swelling of the optic disc due to any reason. Optic neuritis is one of the causes of papilloedema characterized by swelling of disc due to inflammation.

Signs of papilloedema on fundoscopy are:

- Pinkness of the disc followed by blurring and heaping up of its margins.
- Loss of pulsation of retinal veins
- Physiological cup is obliterated, disc engorged with dilatation of its vessels.
- Small hemorrhages often surround the disc.

COMMON CASES OF PAPILLOEDEMA

Raised intracranial pressure
- Cerebral tumor, abscess
- Intracranial hemorrhage, hematoma
- Hydrocephalus, encephalitis
- Idiopathic or benign intracranial hypertension

Optic nerve damage
- Optic neuritis (e.g. multiple sclerosis)
- Ischemic optic neuropathy (e.g. giant cell arteritis)
- Hypervitaminosis A

Venous occlusion
- Central retinal vein occlusion
- Cavernous sinus thrombosis

Systemic disorders affecting retinal vessels
- Malignant hypertension
- Vasculitis (e.g. in SLE)

Metabolic causes
- Hypercapnia (CO_2 narcosis)
- Chronic hypoxia
- Hypocalcemia

Infiltration of optic disc
- Sarcoidosis
- Optic nerve glioma
- Leukemia

Optic neuritis:

- This is an acute inflammatory disorder causing demyelination in the optic nerve near the disc (optic neuritis) or behind the eyeball (retrobulbar neuritis).
- The most common cause of optic neuritis is multiple sclerosis.
- The onset of symptoms is acute with pain in the eye especially on movement and blurring of central vision, a central scotoma is frequently seen causing marked reduction in visual acuity.

Optic atrophy

This is the result of many processes which damage the optic nerve. The atrophied disc appears pale-white in color.

> **COMMON CAUSES OF OPTIC ATROPHY**
> - Previous optic neuritis, ischemia or damage
> - Previous papilloedema from raised intracranial pressure
> - Chronic optic nerve compression
> - Chronic glaucoma
> - Previous trauma
> - Degenerative condition e.g. Friedretch's ataxia.

3. Optic chiasma lesions

Lesions of optic chiasma cause bitemporal hemianopia. Common masses that compress the central part of the chiasma are pituitary neoplasm, craniopharyngioma and secondary neoplasm.

4. Optic tract and optic radiation lesions

Optic tract lesion causes homonymous hemianopia while the lesion of optic radiation produces homonymous quadrianopia. Temporal lobe tumor or infarction is the common causes of lesion.

5. Occipital cortex lesions

Unilateral occipital lesion caused by posterior cerebral artery infarction produces homonymous hemianopia. Bilateral occipital lobe damage caused by tumor, trauma or infarction produces cortical blindness.

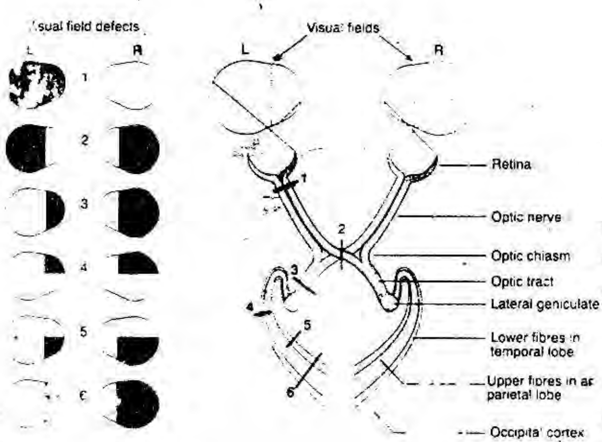


Fig. 14.20 Visual pathways and visual field defects.

DISORDERS OF PUPIL

Normal pupils are round, regular and nearly equal in size. They are constricted in infancy, old age bright light, sleep and convergence. They are dilated in excitement and in the dark.

When light is directed at one eye, both pupils will constrict. The reaction of pupil on the side stimulated is called the <u>*direct light reflex*</u> and constriction of the other pupil is called <u>*consensual light reflex.*</u>

When a near object is viewed, convergence of eye is accompanied by bilateral pupillary constriction referred to as the <u>*accommodation reflex.*</u>

Pupillary light reflex is achieved by a combination of parasymphathetic and sympathetic activity. Parasymphatetic fibers supply constrictor pupillae of the iris and sympathetic fibers supply the dilator pupillae.

Abnormal papillary reflexes

Impairement of pupillary reaction to light may be due to damage to either afferent or efferent sides of reflex arc.

In afferent papillary defect the dysfunction is in retina or optic nerve. The pupil does not have direct light reflex but the consensual light reflex is preserved.

In efferent papillary defect lesion is in oculomotor nerve or ciliary ganglion. One pupil is fixed and dilated and does not respond to light directly, but the contralateral pupil responds consensually.

Abnormal pupillary sizes

<u>Mydriasis</u>

Bilateral mydriasis

- Anxiety
- Thyrotoxicosis
- Antichlinergic drugs such as tricycl antidepressants

Unilateral mydriasis

- Holmes-Adie syndrome
  Unilateral, dilated, irregular, non-reactive pupil in young women due to denervation in ciliary ganglion
- Acute narrow angle glaucoma
- Third nerve palsy

Moisis

Bilatera miosis

- Narcotic overdosage (causing pin point pupil)
- Pontine lesion (causing pin point pupil)
- Miotic drops (e.g. pilocarpine)
- Organophosphorous poisoning
- Argyll-Robertson pupil seen in neurosyphilis

Unilateral miosis

- Horner's syndrome

  Lesions in the sympathetic pathway causes Horner's syndrome that comprises unilateral small pupil (miosis), partial ptosis, enophthalmos and loss of sweating in one half of face (anhydrosis).

CAUSES OF HORNER'S SYNDROME

Cerebrum and brainstem lesions	Sympathetic chain in the neck
• Massive cerebral infarction • Pontine glioma • Lateral medullary syndrome • Coning of the temporal lobe	• Following thyroid/laryngeal surgery • Carotid artery occlusion • Neoplastic infiltration • Cervical sympathectomy
Cervical cord lesions	**Miscellaneous**
• Syringomyelia • Cord tumors	• Congenital • Migranous neuralgia
T1 root lesions	
• Apical bronchial tumor • Apical tuberculosis • Cervical rib • Brachial plexus trauma	

Table 14.18 Clinical manifestations of visual field loss

Site	Common causes	Complaint	Visual field loss	Associated physical signs
Retina/optic disc	Vascular disease (including vasculitis) Glaucoma Inflammation	Partial/complete visual loss depending on site	Altitudinal field defect Arcuate scotoma	Reduced acuity Visual distortion (macula) Abnormal retinal appearance
Optic nerve	Optic neuritis Sarcoidosis Tumour Leber's hereditary optic neuropathy	Partial/complete loss of vision in one eye Often painful Central vision particularly affected	Central scotoma Paracentral scotoma Uniocular blindness	Reduced acuity Reduced colour vision Relative afferent pupillary defect Optic atrophy (late)
Optic chiasm	Pituitary tumours Craniopharyngioma Sarcoidosis	May be none Rarely diplopia ('hemifield slide')	Bitemporal hemianopia	Pituitary function abnormalities
Optic tract	Tumour Inflammatory disease	Disturbed vision to one side of midline	Incongruous contralateral homonymous hemianopia	
Temporal lobe	Stroke Tumour Inflammatory disease	Disturbed vision to one side of midline	Contralateral homonymous upper quadrantanopia	Memory/language disorders
Parietal lobe	Stroke Tumour Inflammatory disease	Disturbed vision to one side of midline Bumping into things	Contralateral homonymous lower quadrantanopia	Contralateral sensory disturbance Asymmetry of optokinetic nystagmus
Occipital lobe	Stroke Tumour Inflammatory disease	Disturbed vision to one side of midline Difficulty reading Bumping into things	Homonymous hemianopia (may be macula-sparing)	Damage to other structures supplied by posterior cerebral circulation

> **CAUSES OF SUDDEN VISUAL LOSS**
>
> - *Amaurosis fugax:* transient unilateral visual loss due to occlusion of central retinal artery due to embolus from carotid artery or aorta.
> - *Hypertensive crises*
> - *Central retinal vein occlusion:* Hypertension, diabetes and glaucoma are common causes.
> - *Optic neuritis*
> - *Toxic optic neuropathy:* resulting from ethambutol, methyl alcohol, and carbon monoxide.
> - *Papilloedema* due to raised intracranial pressure
> - *Retinal detachment*
> - Migraine
> - Factious

III, IV, VI OCULOMOTOR, TROCHLEAR, AND ABDUCENT NERVES

These three cranial innervate the muscles controlling eye movement and pupillary size. Although they have different actions, they are examined together because of their close functional interrelationship.

OCCULOMOTOR NERVE

The nucleus of oculomotor nerve lies in the midbrain. Third nerve supplies superior, inferior medial recti and inferior oblique, levator palpebrae superioris and sphincter pupillae.

Common causes of oculomotor nerve lesion

- Aneurysm of the posterior communicating artery
- Midbrain infarction
- Diabetes mononeuropathy
- Midbrain or pituitary tumor

Clinical features

- Unilateral complete ptosis
- Fixed and dilated pupil (pupil is usually not involved in oculomotor palsy in vasculitis and diabetes)
- Restriction of eye movements (eye facing down and out) however the patient can abduct (abducent) and inward rotate (trochlear) the eyeball.

TROCHLEAR NERVE

Trochlear nerve supplies superior oblique muscle isolated trochlear nerve lesion is uncommon.

Causes of nerve lesion.

Ischemic mononeuropathy (diabetes, hypertension

Head trauma

Clinical features

Diplopia on attempting to look down and away from the affected side.

ABDUCENT NERVE

Abducent nerve supplies the lateral rectus muscle that causes abduction of eye ball. Isolated 6^{th} nerve palsy is common

Causes of nerve lesion

- Raised intracranial pressure
- Diabetes
- Supportive otitis media
- Cerebello-pontine angle tumor
- Cavernous sinus lesions such as aneurysm, pituitary tumor, meningioma
- Pontine stroke.

Clinical features

Diplopia when patient looks towards the side of lesion.

> **CAUSES OF DIPLOPIA**
>
> - Cranial nerve palsy of extraocular muscles
> - Myesthenia gravis
> - Myopathies
> - Myositis
> - Thyroid eye disease
> - Disease oflens or retina

> **CAUSES OF PTOSIS**
>
> - 3^{rd} nerve palsy
> - Horner's syndrome
> - Myasthenia gravis (bilateral)
> - Dystrophia myotonica (bilateral)
> - Local orbital or lid disease

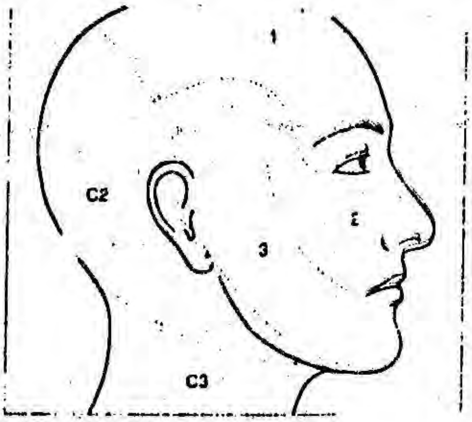
V. TRIGEMINAL NERVE

Trigeminal nerve is mainly sensory but contains some motor fibers.

Sensory function

There are three major sensory branches of trigeminal nerve:

- *Opthalmic branch* supplies sensation to the skin of upper nose, eyelid, forehead, scalp, cornea, and conjunctiva.
- *Maxillary branch* innervates the lower eyelid, upper check, nose, upper lip, mucus membrane of mouth, nose, maxillary, ethmoidal and sphenoidal sinuses, gum, teeth and upper jaw.
- *Mandibular branch* supplies the teeth and gum of lower jaw, mucosa of check and floor of mouth, mucosa of anterior two third of tongue, temporomandibular joint, external and internal ear.



Motor function

Motor branch supplies muscles of mastication, mylohoid and tensor tympani muscles.

CAUSES OF FIFTH NERVE LESION

1. *Brain- stem lesion:*
   Brain stem glioma, multiple sclerosis, infarction and syringobulbia

2. *Cerebello-pontine lesion:*
   Acoustic neuroma, meningioma, secondary neoplasm.

3. *At petrous temporal bone:*
   Spreading infection from middle ear, secondary tumor.

4. *Within cavernous sinus:*
   Aneurysm of the internal carotid artery, lateral extension of a pituitary tumor, cavernous sinus thrombosis secondary tumor.

5. *At trigeminal ganglion:*
   Herpes zoster infection

Clinical features

Complete nerve lesion causes:

- Unilateral sensory loss on the face, tongue and buccal mucosa.
- When motor fibers are damaged the jaw deviates to the side of the lesion when the mouth is opened.
- Diminished corneal reflex.
- Circumoral sensory loss, in brain stem lesion of lower trigeminal nuclei.

TRIGEMINAL NEURALGIA

This is a facial pain syndrome of unknown cause, seen mostly in middle aged and elderly people. It is almost always unilateral.

Clinical features

- Severe paroxysms of knife-like or electric shock- like pain, lasting seconds, occur with distribution of the trigeminal nerve (in maxillary & mandibular division and rarely in ophthalmic division).
- The pain is often brought on by stimulation of a specific "trigger zone" in the face; washing shaving, eating, talking, touching and cold wind may be the stimuli. The pain characteristically does not occur during sleep.
- Spontaneous remission lasts for months or years before recurrence.
- On examination there is no sign of trigeminal nerve dysfunction. The corneal reflex is preserved. Diagnosis is on clinical ground alone.

Medical treatment

Anticonvulsants are effective in most of the cases:

- Carbamazepine (Tegrel 200mg) 600-1200 mg in 3 divided doses is the drug of first choice. Pain relieves within 24 hours.

- Phenyton (Dilantin) 200-40 mg/d, clonazepam (Rivotril) and lamotrigine 400mg/d are also used, but are less effective.

Surgical treatment

Surgical procedures are performed in patient unresponsive to medical therapy.

- Injection of trigeminal ganglion with alcohol or phenol is a common procedure.
- Radiofrequency thrombocoagulation of a branch of the ganglion or sectioning of the sensory root.

POSTHERPETIC NEURALGIA

Herpes zoster – a vesicular skin eruption in dermatomal distribution, accompanied and followed by local pain and tenderness is due to reactivation of varicella-zoster virus in patients with a history of varicella infection.

Management

Acute pain of herpes zoster

The intensity and duration of the cutaneous eruption and the acute pain of herpes zoster are reduced by treatment with:

- Acyclovir (Tab-Zovirax 200mg 4 tab. 5 times daily for 7 days). But this treatment does not reduce the likelihood of postherpetic neuralgia.
- Prednisolone 60mg/d orally for 2 weeks taken during the acute herpetic eruption also reduce the incidence of acute herpetic pain, but have an uncertain effect on post-herpetic neuralgia.

Management of postherpetic neuralgia

- Tricyclic antidepressant such as amitrytiline (tryptanol) 25-150 mg/day is most effective.
- It is more effective if combined with phenothiazine (such as Motival).
- Local application of lidocaine (Lignocaine) gel is effective for pain relief.

VII FACIAL NERVE

The motor nucleus of facial nerve lies in pons, its fibers emerge from lateral pontomedullary junction, then along with VIII nerve and nervus intermedius enter the internal acoustic meatus, then the facial nerve and nervus intermedius enter in facial canal of the temporal bone. Within the temporal bone facial nerve gives branches to the stapedius muscle, tongue for taste, and for lacrimal gland. Facial nerve emerges from stylomastoid foramen and passes through the parotid gland and its branches supply the muscles of facial expression and corneal reflex. The chief function of facial nerve is the supply of motor fibers to the muscles of facial expression.

CAUSES OF FACIAL PALSY

Supranuclear lesion:

Usually due to cerebral infarction.

Characteristics

- Upper motor neuron type facial palsy.
- Hemiparesis of the same side of the body.

Within pons

- Causes are pontine tumors, demyelination and stroke.

Characteristics

- Lower motor neuron type facial palsy.
- Contralateral hemiparesis
- Inability to move eye laterally due to VI nerve lesion.

In the cerebello-pontine angle

Cases are acoustic neuroma, meningioma and secondary tumors.

Characteristics

- Lower motor neuron type facial palsy.
- Fifth, sixth, and eighth nerves are also affected.

Within the petrous temporal bone

Causes are Bell's palsy, trauma, middle ear infection, herpes zoster (Rims Hunt syndrome), and tumors.

Characteristics

- Lower motor neuron type facial palsy
- Loss of taste on anterior two-thirds of the tongue due to damage to the chorda tympani branch.

- Hyperacusis (unpleasantly loud distortion of noise due to paralysis of stapedius muscle).

Within the face itself

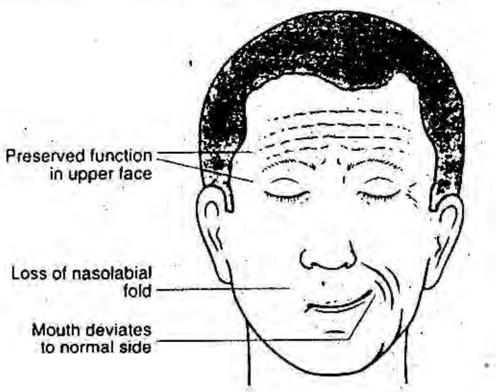
Causes are parotid gland tumors, mumps, sarcoidosis, and trauma.

CAUSES OF FACIAL NERVE PALSIES	
Unilateral	**Bilateral**
Upper motor neurone type weakness • Usually vascular (e.g. stroke) • Cerebral tumor • Multiple sclerosis	**Upper motor neurone type weakness** • Often vascular • Motor neurone disease
Lower motor neurone type weakness • Bell's palsy • Paotid tumors • Head injuries	**Lower motor neurone type weakness** • Sarcoidosis • Myasthenia gravis • Guillan-Barre syndrome • Myotonic dystrophy

TYPES OF LESIONS

Supra-nuclear (upper motor neuron) lesions

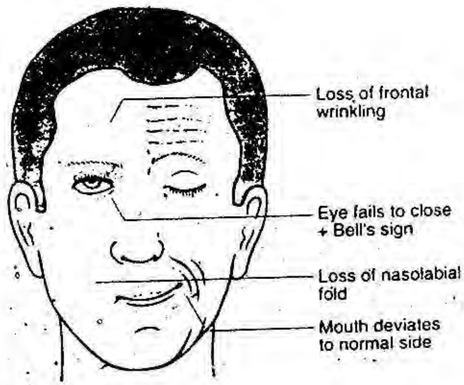
Upper motor neuron lesions are usually due to stroke and manifest as weakness of the lower part of face on the side opposite the lesion. Eye closure and blinking is not affected. Upper face is spared because it gets innervation from both cerebral cortexes. When there is lesion of one hemisphere; nerve supply is affected in lower half only.



In certain cases of supra-nuclear lesions, only those fibers which are concerned with the emotional movement of muscles are effected (incomplete palsy). Therefore when the patient is speaking or smiling involuntarily, his angle of mouth deviates towards healthy side but if patient is asked to show his teeth voluntarily, then there will be no deviation of angle of mouth.

Infra-nuclear (lower motor neuron) lesions

Lower motor neuron lesion causes weakness of all muscles of facial expression on the same side (upper and lower both parts of half face are affected). The reason is that there is bilateral innervation of the muscles of the upper half of the face, i.e. upper half of the face gets its nerve supply from both the hemispheres; therefore a supranuclear lesion only cuts off the nerve impulse to lower half of the face, on the other hand, the infra-nuclear lesion will completely cut off the nerve supply of the respective half of the face. Therefore both the upper and lower parts will be equally involved. The most common cause is Bell's palsy.



BELL'S PALSY

This is a common, acute, isolated facial nerve paralysis believed to be due to viral (often herpes simplex) infection that results in swelling of the nerve within facial canal in the petrous temporal bone. This swelling may be responsible for initial loss of nerve impulse conduction leading to facial paralysis. Bell's palsy is more common in pregnant women and in diabetics.

Clinical features

Symptoms

- There may be pain in the face and around the ear before loss of movement on one side of the face.
- Impairment of taste on the anterior 2/3 of the tongue due to involvement of chorda tympani fibers in some patients.
- Marked unilateral facial weakness
- Dribbling of saliva and water from affected side.
- Collection of food in the mouth on paralyzed side.

Signs

- Loss of wrinkling on the affected half of forehead.
- Inability to close the eye.
- *Bell's phenomenon:* upward rotation of the eyeball on trying to close the affected eye.
- Flattening of the nasolabial fold.
- Loss of retraction of the angle of the mouth, while showing his teeth.

Tests for conformation

1. Wrinkling of the forehead: Ask the patient to look upward without tilting his head. Horizontal lines will appear on the forehead. Compare the creases on two halves of the forehead. If one half of the forehead is flat, this indicates lower motor neurone paralysis of facial nerve of the same side, but if the lower half is only paralyzed it indicates upper motor neuron lesion.

2. Closure of the eyes: Ask the patient to close his eyes forcibly. Now try to open the eyes and note the force needed for either side. Eye of paralyzed side will either not close properly or will open up with slight force. When the patient tries to close the eyes, eyeball moves upward & medically, it is called "Bell's Phenomenon".

3. Inflation test: Ask the patient to inflate his mouth with air and blow out his cheeks. Tap with the finger, on each inflated cheek; air can be made to escape from the mouth more easily on the week or paralyzed side.

Management

About 70-80% of patients with Bell's palsy recovers spontaneously without treatment, however it may take several days to several months. Poor prognostic factors are:

- Severe pain at onset
- Complete palsy at onset
- Old age

EMG and nerve conduction studies may provide guidance about prognosis.

Medical treatment

- Prednisolone (Tab. Deltacortil) 60mg/d for 3 days, tapering over the next 7 days, beginning within 5 days after the onset of palsy, is said to increase the proportion of patients who recover completely. Steroids reduce edema of the facial nerve, and may limit damage and speed recovery.
- Some physicians use acyclovir also.

Surgical [illegible]

- *Eye pad:* if closure is affected eye pad is applied to prevent exposure keratitis. Tarsorrhaphy (suturing of upper to the lower lid) may be required.
- *Cosmetic surgery*: anastomosis of the lingual nerve to the facial nerve is sometimes indicated if there is no recovery after a year.
- Surgical decompression of nerve for acute attack is not beneficial.

Ramsay hunt syndrome

Herpes zoster of geniculate ganglion causes facial palsy with herpetic vesicles in the external auditory meatus, this combination is called Ramsay Hunt syndrome.

VIII VESTIBULOCOCHLEAR NERVE

The nerve has two parts cochlear and vestbular parts.

COCHLEAR NERVE:

It is a sensory nerve that arises from organ of corti in the cochlea and pass to the cochlear nuclei in the pons. The function of cochlear nerve is hearing.

- Features of cochlear nerve lesions are sensorineural deafness & tinnitus.
- Impaired hearing is best studied using pure-tone audiometry and brain stem evoked potentials. Bedside tests are performed with tuning fork such as Rinne's and Weber's test.

CAUSES OF SENSORINEURAL DEAFNESS

End organ
- Advancing age
- Occupational acoustic trauma
- Meniere's disease
- Drugs e.g. gentamicin, neomycin

Eighth-nerve-lesion
- Acoustic neuroma
- Cranial trauma
- Inflammatory lesions:
- Tuberculous meningitis
- Sarcoidosis
- Neurosyphilis
- Carcinomatous meningitis

Brainstem lesions (rare)
- Multiple sclerosis
- Infarction.

VESTIBULAR NERVE:

It is a sensory nerve that arises from three semicircular canals and pass to the vestibular nuclei in the pons. The vestibular nuclei are connected to the cerebellum, nuclei of ocular muscles, temporal lobes and spinal cord.
Vestibular nerve is related to equilibrium.

- Features of vestibular nerve lesion are: Vertigo, vomiting, nystagmus, and loss of balance.
- Caloric tests are used to assess function of the labyrinth.

VERTIGO

Abnormal perception of movement of the environment is called vertigo. Patient feels spinning of environment. It indicates disturbance of vestibular apparatus, vestibular nerve or brainstem.

Types

Central vertigo
When the vertigo develops due to cerebellum or brainstem lesion, it is called central vertigo. Usually it is not associated with deafness or tinnitus. It may occur with or without nystagmus. Central vertigo may be associated with brainstem or cerebellar signs, such as motor or sensory deficits, hyperreflexia, extensor planter response, dysarthritis, or limb ataxia.

Peripheral vertigo:
When the lesion is in the vestibular apparatus in inner ear or 8th nerve, it is called peripheral vertigo. It is usually associated with *deafness and tinnitus*. Peripheral vertigo is always associated with *nystagmus*.

Benign positional vertigo
It is the vertigo precipitated by head movements, usually in a particular direction. It is transient lasting for seconds or minutes. Sometimes it is associated with vestibular neuronitis.

Causes of vertigo

Without deafness and tinnitus
- Viral vestiular neuronitis
- Multiple sclerosis
- Benign positional vertigo
- Migraine multiple sclerosis
- Vertebrobasillar ischemia
- Acute cerebellar lesion
- Anti-epilepsy drug intoxication
- Alcohol intoxication

With deafness and tinnitus
- Meniere's disease
- Skull fracture
- Chronic otitis media
- Acoustic neuroma
- Ototoxic drugs such as aminoglycosides

VESTIBULAR NEURONITIS

This is the most common cause of isolated vertigo (without deafness and tinnitus). It is believed to follow or accompany viral infections that affect the labyrinth or vestibular nerve. It lasts for several days or weeks but is self-limiting.

Treatment is with vestibular sedatives such as prochlorperzone (Stemetil), cinnarizine (Stugeron), betahistine (Serc 16 mg TDS).

NYSTAGMUS

Nystagmus is a rhythmic oscillation of the eyes. It is a sign of disease of either the ocular or the vestibular system and its connections.

Types

There are two types of nystagmus:

Jerk nystagmus

- It is the usual nystagmus of neurological disease and has two components, *fast and slow*.
- Horizontal or rotatory nystagmus may be due to peripheral lesion (in middle ear) or central lesion (in 8th nerve, brainstem cerebellum and their connections).
- Vertical nystagmus is only caused by central lesion.

Pendular nystagmus

- Pendular nystagmus means to and fro movements, which are similar in amplitude and velocity.
- It occurs in ocular diseases in which there is long - standing severe visual impairment.

IX, X GLOSSOPHARYNGEAL AND VAGUS NERVES

These nerves are grouped together because they pass through the jugular foramen and tend to be affected in a group.

GLOSSOPHARYNGEAL NERVE

This is a mixed nerve arises from medulla and leaves skull through jugular foramen alone with the vagus and accessory. It supplies the following muscles.

- Sensory: tonsillar fossa, pharynx, taste, (posterior one third of tongue)
- Motor: Stylopharyngeus muscle
- Autonomic: Parotid gland

VAGUS NERVE

- Motor: Pharynx, larynx (including vocal cords) and upper esophagus
- Sensory: Larynx, dura mater of posterior cranial fossa
- Autonomic: heart, lung and abdominal viscera

Clinical features of abnormalities IX and X

1. *Dysphagia:* lesion of IX and X nerve causes difficulty in swallowing due to palatal and pharyngeal muscle palsy.
2. *Loss of gag reflex*
3. *Dysphonia:* hoarseness due to weakness of muscles of vocal cords.

- Isolated palsy of each nerve is unusual, disease at the jugular foramen affects both nerves and sometimes XI also.
- Unilateral IX nerve lesion causes diminished sensation on the same side of pharynx.
- Unilateral X nerve palsy produces ipsilateral failure of voluntary and reflex elevation of soft palate.
- Bilateral combined lesion of IX and X nerves cause weakness of elevation of the palate, weakness of laryngeal muscles and loss of gag reflex. Patient complains of difficulty in swallowing, hoarseness, nasal regurgitation and choking particularly with liquids.

CAUSES OF IX AND X NERVE LESION

Unilateral IX and X nerve lesion
- Tumors of skull base
- Fracture of skull base

Recurrent laryngeal ranch of X
- Bronchial carcinoma
- Mediastinal lymphoma
- Aortic arch aneurysm

Bilateral X nerve lesion
- Progressive bulbar palsy (in motor neuron disease)
- Pseudobulbar palsy in stroke, and multiple sclerosis

XI ACCESSORY NERVE

This is motor nerve to trapezius and sternomastoid. It arises in medulla and leaves skull through jugular foramen with ninth and tenth nerve.

Clinical features
1. Weakness of trapezius (loss of shoulder shrugging).
2. Weakness of sternomastoid (loss of rotation of the head and neck to the opposite side).

XII HYPOGLOSSAL NERVE

It is motor nerve to tongue, arises from medulla and leaves skull through the anterior condylar foramen.
- Bilateral upper motor neuron (UMN) lesion causes slowness of the tongue movements and the tongue cannot be protruded very far. There is no fasciculation.
- Lower motor neuron (LMN) lesion causes unilateral weakness, wasting and fasciculation. When protruded the tongue deviates towards the *weaker side.*

BULBAR AND PSEUDOBULBAR PALSIES

The lower cranial nerves 9, 10, 11, and 12 are frequently affected bilaterally, producing dysphagia and dysarthria.

Bulbar palsy

The term "bulbar palsy" is used if this results from lower motor neuron lesions (LMN) either in medulla (bulb) or from bilateral lesions of the lower cranial nerves outside the brain stem.

Pseudobulbar palsy

Pseudobulbar palsy describes bilateral upper motor neuron (UMN) lesions of lower cranial nuclei producing weakness and slowing of movements of bulbar muscles (tongue and pharyngeal muscles). Clinical features are slow, spastic tongue (but not wasted), dysarthria and dysphagia. The gag reflex and palatal reflex are preserved. The jaw jerk is exaggerated. Emotional liability (inappropriate laughing or crying) often accompanies pseudobulbar palsy.

CAUSES OF BULBAR AND PSEUDOBULBAR PALSY

	Bulbar	Pseudobulbar
Genetic	Kennedy's disease	
Vascular	Medullary infarction	Bilateral hemisphere (lacunar) infarction
Degenerative	• Motor neuron disease. • Syringobulbia	Motor neuron disease
Inflammatory /infective	• Myasthenia • Guillain- Barre • Lyme disease • Vasculitis	• Multiple sclerosis • Cerebral vasculitis
Neoplastic	• Brain- stem glioma. • Malignant meningitis	High brain-stem tumors

PARKINSONISM

Parkinsonism is a chronic and progressive clinical syndrome due to lesion in the basal ganglia and is characterized by tremors, muscle rigidity and hypokinesis (slowness in initiating and repeating voluntary movements, despite normal muscular strength).

INCIDENCE

- Age: above 50 years 1-2/1000 population
- Sex: equally distributed
- Smoking: less common in smokers

ETIOLOGY

1. **Idiopathic**
   Also called paralysis agitans or Parkinson's disease.
2. **MPTP**
   Methyl phenyl- tetrahydro - pyridine (MPTP) causes severe Parkinsonism, it is suggested that idiopathic disease may be due to an environmental toxin like MPTP.
3. **Drugs**
   Phenothiazines e.g. haloperidol. Reserpine and metocloperamide also cause Parkinsonism.
4. **Trauma:**
   Repeated head injury (punch drunks syndrome)
5. **Viral infections:**
   Encephalitis lethargica

PARKINSON'S DISEASE

(Idiopathic Parkinsonism)

Pathophysiology

The abnormalities seen in Parkinson's disease are:

- Depletion of pigmented dopaminergic neurons in the substantia nigra.
- Progressive cell degeneration in substantia nigra.
- Presence of neuronal eosinophilic inclusion bodies (Lewy bodies) in nigral cells

These changes result in reduced dopaminergic output from subtantia nigra to the globus pallidus resulting in inhibition of activation of cerebral cortex causing bradykinesia (slowness).

CLINICAL FEATURES

Initial symptoms

Tiredness, mental slowness, depression, aching limbs and small handwriting (micrographia).

Classical symptoms

1. **Tremor** – tremor is typically present at rest that increases with emotional stress and improves during voluntary activity. It commonly begins in the hand and foot; where it takes the form of rhythmic flexion-extension of fingers or of hand or foot----- or rhythmic supination – pronation of forearm (pill rolling movements). It frequently involves mouth and chin. Tremor may be confined to one side of body for months or years before it becomes generalized.

2. **Rigidity** – Rigidity or increased tone causes stiffness, and flexed posture. The resistance or hypertonia is typically uniform through out the range of movement *(lead-pipe rigidity)*. When combined with tremor the smooth lead-pipe rigidity is broken up into a jerky rigidity called cogwheel rigidity. Simultaneous active movement of the opposite limb increases the tone of the side under examination.

3. **Hypokinesia** – hypokinesia means slowness of voluntary movements and a reduction in automatic movements, such as swinging the arms while walking. The patient's face is relatively immobile (*mask - like facies*) with infrequent blinking. Patients have difficulty in fine and rapidly alternating movements such as fastening buttons or writing.

4. **Abnormal gait and posture**
   The patient finds difficult to get up from bed or chair and tends to adopt a flexed posture on walking. The gait is characterized by small, shuffling steps and absence of arm swing (shuffling gait). In advanced cases, the patient tends to walk with increasing speed to prevent a fall (festinating gait) because of the altered center of gravity that results from the abnormal posture.

5. **Speech and cognition**
   Speech is initially monotonous then progress to tremulous slurring dysarthria. Cognitive function is preserved, however dementia may develop in late stages. *Glabellar tapping* produces sustained blinking of eyes. Depression and hallucinations are frequent.

DIFFERENTIAL DIAGNOSIS

There is no laboratory test for the diagnosis of the disease. The diagnosis is made on clinical grounds alone. Other conditions that may cause slowing., rigidity and tremor should be ruled out before diagnosis of Parkinson's disease such as:

- Hypothyroidism
- Depression
- Drug induced Parkinsonism
- Multi-infarct dementia
- Alzheimer's disease
- Shy-Drager syndrome
- Essential benign familial tremor
- Striatonigral degeneration
- Progressive supranuclear palsy
- Cortical basal ganglionic degeneration
- Wilson's disease
- Hungtington's disease

PHYSICAL ABNORMALITIES IN PARKINSONISM

General
- Expressionless face
- Greasy skin
- Soft, rapid, indistinct speech
- Flexed posture
- Impaired postural reflexes

Gait
- Slow to start walking
- Shortened stride
- Rapid, small steps, tendency to run (festination)
- Reduced arm swing, impaired balance on turning

Tremor
- *Resting tremors*
  Usually first in fingers/thumb
  Coarse movements, flexion/extension of fingers
  Abduction/adduction of thumb
  Supination/pronation of forearm
  May affect arms, legs, feet, jaw, tongue
  Intermittent, present at rest and when distracted
  Diminishing on action
- *Postural tremors*
  Less obvious, faster, finer amplitude
  Present on action or posture, persists with movement

Rigidity
- Cogwheel type, mostly upper limbs
- Plastic (lead pipe) type, mostly legs

Bradykinesia
- Slowness in initiating or repeating movements
- Impaired fine movements, especially of fingers

MANAGEMENT

The treatment of Parkinsonism is directed toward restoring the dopaminergic: cholinergic balance in the striatum by blocking the effect of acetycholine with antichloinergic drugs or by enhancing dopaminergic transmission.

Anticholinergic agents

They have a useful effect on tremor and rigidity but do not help in hypokinesia. They can be prescribed early in the disease before hypokinesis is the problem, but should be avoided in elderly (over 60 years) because they can cause confusion and hallucination. Other side effects are dry mouth, urinary retention and defective accommodation reflex.

- Benzhexol (Pacitane 2mg) 0.5-2mg TDS
- Procyclidine (Kamadrin 5mg) 2.5-10mg TDS

Amantadine (Symmetrel)

It potentiates the release of endogenous dopamine. It is used in mild cases given alone or in combination of anticholinergic agent. Side effects are uncommon, if occur they are restlessness, confusion and cardiac arrhythmia.

Dose: Tab Symmetrel 100mg B.D.

Levodopa

Levodopa is converted in dropamine & thus replaces the dopamine deficiency in brain. It ameliorates all the major clinical features of Parkinsonism. But the problem is that 90% levodopa given orally is decarboxylated peripherally in the GIT and blood vessels to dopamine, therefore only small proportion of levodopa reaches the brain (dopamine itself cannot cross blood-brain barrier). This peripheral conversion is responsible for the high incidence of side effects (nausea, vomiting, vasodilatation). This problem is largely overcome by giving along with levodopa a peripheral acting decarboxylase inhibitor e.g. carbidopa & benserazide.

- Levodopa 250mg + carbidopa 25mg → **Sinemet** start with ½ tab TDS then increase to 1 TDS
- Levodopa 250 mg + benserazide 50mg → **Madopar** start with ½ TDS then increase to 1TDS.

The dose is increased gradually until either an adequate improvement has taken place or side-effects limit further increase in dose. Levodopa should be taken 1 hour before or 2 hours after meal to maximize absorption.

Side effects
Nausea, vomiting, postural hypotension and occasionally cardiac arrhythmia and abnormal movements (dyskinesia).

Contraindications
Narrow angle glaucoma, psychosis, peptic ulcer and patient taking monoamine oxidase inhibitors.

Bromocripitine (Dopamine agonists)
It stimulates postsynaptic dopamine receptors D_2. It is slightly less effective than levodopa but is less likely to cause dyskinesia. It is recommended that start with Sinemet and then add bromocriptine and then increase its dose gradually.

Dose *(Tab Parlodel 2.5mg)* week-1 half tablet at bedtime, week- 2 one tablet at bedtime, week -3 one tablet BD, week - 4 one tablet TDS, then gradually increase to 10-40 mg in three divided doses.

Side effects: nausea, vomiting, delusion or hallucination.

Contraindications: recent myocardial infarction peptic ulcer, peripheral vascular disease and psychiatric illness.

Selegiline (Jumex)
Selegiline is a monoamine oxidase type B inhibitor and inhibits the metabolic breakdown of dopamine. It is the cytoprotective agent and may delay the progression of disease. It is not good to control symptoms, therefore should be used for mild disease. Usually it is used as adjunctive therapy in patient taking levodopa.

Dose: Tab. Jumex 5mg after breakfast and lunch.

Surgical treatment
Surgical treatment of parkinsonism by thalamotomy or pallidotomy is often helpful when patients becom unresponsive to medical measures or develop intolerable side effects of anti-Parkinsonian medications.

THERAPEUTIC STRATEGY IN PARKINSON'S DISEASE

Stage	Features	Drugs
Early	Tremor Regidity	*Under age 65* • Anticholinergics • Amantidine *Over age 65* • Avoid anticholinergics • Amantidine
Moderate	Tremor Rigidity Hypokinesis	• Levodopa • Anticholinergics • In younger patients consider low dose bromocriptine+ levodopa
Severe	Tremor Rigidity Hypokinesis Dyskinesia Fluctuation	Frequent small doses of levodopa ± selegine ± low dose bromocriptine

MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is a common disease of unknown cause in which there are multiple areas of demyelination within the brain and spinal cord. Peak incidence is between ages 20-40. Women are affected twice as often as men.

ETIOLOGY

Exact cause is unknown, immune mechanism against CNS myelin sheath is suggested due to presence of increased levels of activated T-lymphocytes in the CSF, and increased immunoglobulin synthesis within the CNS. Myelin sheaths of peripheral neves are not affected.

PATHOLOGY

The essential features are plaques of demyelination (damage of myelin sheath with inflammation and subsequent fibrosis) in multiple areas of CNS having predilection for the following sites:

- Periventricular region
- Optic nerve
- Brainstem and its cerebellar connections
- Cervical spinal cord

Demyclination may impair nerve conduction (conduction block) that lowers the efficiency of CNS function. Demyelination may also cause ectopic impulse generation that causes paraesthesias such as Lhermitte's phenomenon (electric-like sensations in spine and limb on flexion of neck).

CLINICAL FEATURES
Onset may be dramatic or very mild and slow.

Initial or presenting features

Blurring of vision due to optic neuritis

- Optic neuritis produces variable visual loss such as blurring which may remain mild or progress to severe visual loss.
- Optic neuritis is usually unilateral but may be bilateral.
- Fundoscopy may show papilloedema. Fundoscopy may be normal if the lesion is retrobulbar.
- Repeated attacks of optic neuritis may lead to optic atrophy that appears pale on fundoscopy.

Weakness in one or more limbs
Weakness may present as fatigue, foot drop or disturbance of gait. On examination there is hyperreflexia, hypertonia, extensor planter resonse and absence of superficial abdominal reflex, all indicative of pyramidal tract disease.

Sensory symptoms (paraesthesias)
Sensory symptoms include paraesthesia such as feeling of pins, tingling, painful burning or numbness often beginning in a focal area of a limb.

Ataxia
Cerebellar involvement results in ataxia of gait and limb. In advanced MS, cerebellar dysarthria (scanning speech) is common.

Diplopia
Double vision (diplopia) may be due to internuclear opthalmoplegia or sixth nerve palsy.

Urinary symptoms
Urinary bladder urgency, hesitancy or incontinence may present at onset. Constipation, fecal urgency or bowel incontinence occurs usually in advanced MS.

Initial or presenting features of MS

- Blurring of vision
- Weakness in one or more limbs
- Paraesthesias
- Ataxia
- Diplopia
- Urinary symptoms

- Multiple sclerosis worsens transiently following exposure of patient to heat, stress, or infection.

Subsequent course

There may be an interval of months or years after the initial episode before further neurologic symptoms appear.
Based on its course, the disease is divided into the following three patterns:

1. Relapsing remitting MS
Around 80% of patients have a relapsing and remitting clinical course characterized by recurrent attacks of neurologic dysfunction, the attacks generally evolve over days to weeks and may be followed by complete, partial, or no recovery. Recovery usually occurs within weeks to several months.

2. Secondary progressive MS
The disease has relapsing- remitting course at first but evolves to be progressive. The progressive phase may begin shortly after disease onset or be delayed for several years or decades.

3. Primary progressive MS
It is characterized by gradual progression of disability from the onset of disease.

End-stage multiple sclerosis

- Patient is severely disabled with spastic paraparesis, ataxia, optic atrophy, nystagmus, pseudobulbar palsy, incontinence of urine, dementia.
- Death occurs usually due to bronchopneumonia or renal failure.

PROGNOSTIC FACTORS OF MULTIPLE SCLEROSIS

Good prognostic factors

- Onset before age 40
- Visual or sensory symptoms alone at initial presentation, no pyramidal or cerebellar dysfunction.
- Relapsing-remitting course
- Minimal neurologic impairment 5 years after onset.

Poor prognostic factors

- Truncal ataxia
- Severe action tremor
- Primary progressive disease pattern

CLINICAL DIAGNOSTIC CRITERIA FOR MULTIPLE SCLEROSIS

Clinically definite (requires all)

- Age < 60 years
- History or signs of deficits in two or more anatomical sites in CNS.
- On CNS examination abnormal signs are present which indicate white matter involvement
- CNS involvement in one of two patterns
  Relapsing and remitting: two or more episodes lasting at least 24 hours and > 1 month apart.
  Progressive: slow and/or stepwise progression over at least 6 months.
- No other explanation of symptoms

Clinically probable

- Relapsing and remitting symptoms with one neurological sign commonly associated with MS or
- Documented single episode with partial or complete recovery with signs of multifocal white matter disease and no other explanation.

Clinically possible

- Relapsing and remitting symptoms without documented or objective sign of establish more than one anatomical site of CNS involvement.
- No other explanation for clinical features

INVESTIGATIONS

CSF examination

- Increased CSF lymphocytes but less than 50 cells/ μL.
- Total CSF protein is normal but the level of 1gG is increased.
- *CSF electrophoresis* shows presence of *oligoclonal bands* of 1gG antibodies indicating the production of antibody against unknown antigens within the CNS. Two or more oligoclonal bands are found in *75 – 80%* of MS patients. The bands may be absent at onset but increase with time. Oligoclonal bands are not specific to MS, they indicate intrathecal inflammation and occur in other conditions also.

MRI

MRI is very sensitive to detect lesions of brain and spinal cord in MS. Multiple plaques are visible principally in the periventricular region, brainstem, and cervical cords.

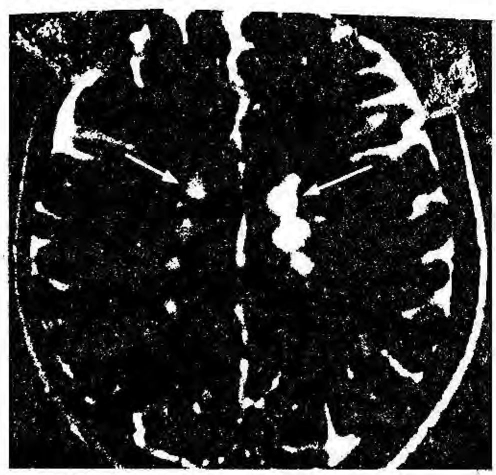


Fig 18.22
Multiple areas of high signal (arrows) on T2-weighted images in the periventricular white matter in a patient with multiple sclerosis

Electrophysiological tests

Visual evoked potential and brainstem auditory evoked potential are delayed when there is involvement of optic nerve and brainstem respectively.

Routine tests

Blood CP, plain x-ray, EEG and urine analysis are unhelpful in diagnosis.

> **INVESTIGATIONS IN A PATIENT SUSPECTED OF HAVING MULTIPLE SCLEROSIS**
>
> - *Exclude other structural disease and identify plaques of demyelination:*
>
>   Imaging (MRI, myelography)
> - *Demonstrate other sites of involvement*
>   Visual evoked potentials
>   Other evoked potentials
> - *Demonstrate inflammatory nature of lesion(s)*
>   CSF examination (cell count, protein electrophoresis)
> - *Exclude other conditions*
>   Chest radiograph, serum angiotensin-converting enzyme (ACE), and serum B_{12} antibodies.

DIAGNOSIS & DIFFERENTIAL DIAGNOSIS

Diagnosis of MS is clinical as it is relapsing remitting disease with specific features. Problems in diagnosis come on the onset of disease when no one knows about relapsing remitting nature of disease or when the disease starts primary progressive pattern. MRI helps in diagnosis. The other possibilities that come in mind are:

1. SLE
2. Stroke – more sudden onset than multiple sclerosis.
3. Friedreich's ataxia – gradually progressive without remission (while multiple sclerosis is relapsing & remitting disease).
4. CNS sarcoidosis
5. Bechcet's syndrome--- along with optic neuropathy and myelopathy it also has oral and genital ulcers and uveitis.
6. Sjogren's syndrome.

MANAGEMENT

The treatment of multiple sclerosis can be divided into two categories.:

- Disease modifying therapy
- Symptomatic treatment or supportive therapy.

Disease modifying therapy

Initial attack and acute relapse

Treatment of first attack or acute relapse later- on is treated with steroids. Initially intravenous methylprednisolone is given for 3 days then oral prednisolone for next 18 days

Methylprednisolone (Inj. Solu-medrol 250 mg mixed in 250ml dextrose water give within 1-2 hours 6 hourly for 3 days followed by oral prednisolone (Deltacortil) 1mg/kg/day in single dose for next 13 days then taper and stop after next 4 days.

Prophylaxis against relapses

One of the following the drugs are used to prevent relapse in MS.

- Interferon β1a 6 million units 1/M once a week.
- Interferon β1b 8 million units S/C every other day.
- Copolymer 1 20mg S/C daily.

They reduce annual exacerbation rates by approximately one third.

Treatment should be discontinued in patients who are not responding and experience frequent attacks or gradual progression of disability for 6 months.

Secondary progressive MS

One of the following drugs may be used for secondary progressive pattern. They should not be used in primary progressive pattern, age more than 60 years and in bed-ridden patient because their side effects are more than their benefits.

- Methotrexate 7.5mg orally once a week for up to 2 years.
- Azathioprine 2-3 mg/kg daily.
- Cyclophosphomide in case of rapid and progressive neurological deficits.

Supportive therapy

Spasticity

- Physiotherapy
- Baclofen (Tab. Lioresal 10mg)
- Diazepam
- Clonazipam
- Dantrolene

Painful paraesthesias, trigeminal neuralgia

- Carbamazepine (Tegrel) 100-1200mg/d in 3 divided doses.
- Amitriptyline

Ataxia

- Isoniazid 600-1200 mg in divided doses
- Clonazipam 2-8 mg in divided doses

Urinary incontinence
Anticholinergic drugs

Urinary retention
Cholinergic drug such as bethanecol 10mg TDS.

Constipation
Laxatives and enemas

Fecal incontinence
Low fiber diet to reduce the bulk of feces

PREGNANCY AND MS

Pregnant patient experience fever attacks during gestation but more attacks in the first 3 months after parturition.

INTRACRANIAL TUMORS

Relative frequency of common intracranial tumors on the basis of clinical presentation

Tumour	*Relative frequency*
Primary malignant (gliomas) • Astrocytoma • Oligodendroglia	35%
Benign • Meningioma • Neurofibroma (schwannoma)	15%
Metastases • Bronchus • Breast • Stomach • Prostate • Thyroid • Kidney	50%

Primary malignant tumors
These malignant tumors originate in neuroglia usually within cerebral hemispheres. They virtually never metastasize outside the CNS. They tend to spread only by direct extension.

- Astrocytomas: arise from astrocytes
- Oligodendrogliomas: arise from oligodendroglia.

Benign tumors

- *Meningioma*: arise from arachnoid matter .
- *Neurofibroma:* arise from Schwann cells.

Table 14.42 Primary malignant intracranial tumours

Histological type	Common site	Age
Glioma (astrocytoma)	Cerebral hemisphere Cerebellum Brain stem	Adult Childhood/adult Childhood/young adult
Oligodendroglioma	Cerebral hemisphere	Adult
Medulloblastoma	Posterior fossa	Childhood
Ependymoma	Posterior fossa	Childhood/adolescence
Microglioma (cerebral lymphoma)	Cerebral hemisphere	Adult

Table 14.43 Primary benign intracranial tumours

Histological type	Common site	Age
Meningioma	Cortical dura Parasagittal Sphenoid ridge Suprasellar Olfactory groove	Adult
Neurofibroma	Acoustic neuroma	Adult
Craniopharyngioma	Suprasellar	Childhood/adolescence
Pituitary adenoma	Pituitary fossa	Adult
Colloid cyst	3rd ventricle	Any age

CLINICAL FEATURES

Clinical features depend on site & rate of expansion of the tumor, producing signs & symptoms in three co-existing ways.

1. **By direct local effect** on adjacent cerebral tissue, which are either destroyed or suffer impairment of function from infiltration, pressure or cerebral edema.
2. **By secondary effects of raised intracranial pressure** and shift of intracranial contents.
3. By provoking either generalized or partial **seizures.**

Local effects

Mass lesion causes progressive deterioration of function of surrounding brain tissue. Following are the examples:

- *Left frontal meningioma:* It causes vague disturbance of personality & impairment of intellectual function over several months. When speech area is affected, an expressive aphasia will develop.

- Right parietal glioma involving the fibers of the optic disc radiation will cause homonymous field defect, cortical sensory loss, hemiparesis & partial seizure may develop.
- Neurofibroma of left eighth nerve sheath (acoustic neuroma) will cause progressive perceptive deafness vertigo, numbness of left of the face, facial weakness and cerebellar ataxia.

Raised intra cranial pressure

This may be caused by the tumor mass, reactive cerebral edema or obstruction of CSF pathways.

The features of raised intracranial pressure are:

1. Headache

- It is most severe in the morning, felt diffusely over the cranium.
- It is aggravated by activities such as coughing, bending & straining, which further increase the intracranial pressure.
- It occurs due to distortion of or traction on nearby arteries, venous sinuses or meninges which are pain sensitive.

2. Vomiting

It is sudden, projectile & not preceded by nausea.

3. Visual disturbances

Episodes of transient blindness in both eyes lasting only a few seconds.

4. Impairment of conscious level

It ranges from listlessness and drowsiness to Coma.

5. Papilloedema:

Swelling of the optic disc is an important sign of raised intracranial pressure.

Features of intracranial contents shift due to raised intracranial pressure.

1. Distortion of brain stem due to shift of midline structures causes impairment of consciousness.
2. Compression of medulla by herniation of the cerebellar tonsils through foramen magnum (coning) results in impairment of consciousness, respiratory depression, bradycardia, decerebrate posturing and death.
3. *False localizing signs,* which are false; only because they do not point directly to the site of mass.

Examples of false localizing signs are:

- 6th nerve palsy: first on side of mass and then bilaterally as the nerve is compressed due to expanding tumor.
- 3rd nerve palsy as the uncus of the temporal lobe herniates causing nerve compression.
- Hemiparesis of the same side due to compression of contralateral cerebral peduncle (it is a good example for understanding the false localizing sign because clinician expect hemiparesis of body opposite the tumor side while the hemiparesisis on the same side due to compression of opposite side of brain).

FALSE LOCALIZING SIGNS OF A MASS LESION

- Pupillary dilatation (ipsilateral to lesion)
- 6th cranial nerve lesion (unilateral or bilateral)
- Hemiparesis (ipsilateral to lesion)
- Bilateral extensor plantar responses

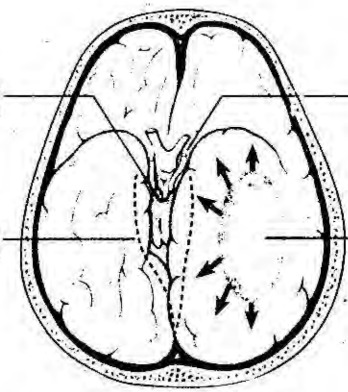


Fig. 14.44 Cerebral tumour displacing medial temporal lobe and causing pressure on the mid-brain and 3rd cranial nerve.

Seizures

Infiltration of tumor cells of an area of cerebral cortex often invokes excitatory response in neighboring neurons and may result in partial or generalized seizures. Partial seizure in adult life should always suggest the possibility of brain tumor.

INVESTIGATIONS

Investigations for cerebral tumor should be considered in any patient presenting with:

- Recent onset of progressive neurological dysfunction.
- S/S suggesting raised intracranial pressure
- Development of seizures over the age of 18.

CT scan:

CT contrast helps in localizing the site and size of tumor, although it provides some clue about the nature of tumor, yet cerebral abscess, infarction, and benign and malignant tumors should be the differential diagnosis.

MRI:

MRI is of particular value for tumors of posterior cranial fossa and brainstem, the areas in which CT scan has a relatively poor resolution.

Plain x-ray skull

It has little screening value except the lesions of vault. It gives important information about changes in dorsum sellae and clenoid processes in pituitary tumor.

X-ray chest:

It is performed to see primary tumor or metastasis

Biopsy

Biopsy via burr-hole or craniotomy is required for histologic diagnosis of hemispheric malignancy.

MANAGEMENT

Medical

It is only supportive

For cerebral edema around tumor & raised intracranial pressure

(a) Dexamethasone 8 mg 12 hourly orally or injectable.
(b) Mannitol 20% 200 ml over 60-90 minutes

Surgical

It is the curative treatment, some tumors can be removed without brain damage, some are technically difficult to remove and gliomas can rarely to excised due to spread of the tumor. Meningiomas and acoustic neuromas can be completely removed without major damage to the surrounding brain structure. Pituitary adenoma can be removed through trans-sphenoidal route.

Radiotherapy and chemotherapy

Radiotherapy is carried out for gliomas and radiosensitive metastases e.g. ependymomas, meduloblastomas, to prevent recurrence after pituitary adenoma after surgery. Chemotherapy has little value in majority of primary or secondary brain tumors.

PROGNOSIS

Benign tumors that can be operated have good prognosis while in malignant tumors two years survival is less than 50%.

HYDROCEPHALUS

Hydrocephalus is an increase in CSF volume, usually resulting from impaired absorption, and rarely from excessive secretion. This obstruction of the cerebrospinal fluid circulation results in dilatation of the ventricular system of brain

TYPES

Communicating hydrocephalus

If obstruction is outside the ventricular system (usually in basal cistern, it is called communicating hydrocephalus) Ventricular CSF can communicate with the subarachnoid space. Ventriculoatrial or ventriculoperitoneal shunting of CSF may result in prompt relief of symptoms.

Causes

- Bacterial meningitis (esp. tuberculous)
- Sarcoidosis
- Subarachnoid hemorrhage
- Head injury
- Idiopathic (normal pressure)

Non-communicating hydrocephalus

Hydrocephalus resulting from obstruction within the ventricles is called non-communicating hydrocephalus.

Causes

- Tumors
- Arnold- Chiari malformation
- Aqueduct stenosis
- Cerebellar abscess
- Cerebellar or brain- stem hematoma

CLINICAL FEATURES

Hydrocephalus in infants and young children

In infants it could be congenital defect, or acquired after meningitis or cerebral hemorrhage.

Acute onset: presents with irritability, impaired consciousness and vomiting.

Gradual onset: presents with mental retardation and failure to thrive.

Hydrocephalus in adults

Acute onset: presents with signs and symptoms of raised intracranial pressure such as headache, vomiting, papilloedema and deterioration of conscious level.

Gradual onset: presents with dementia gait ataxia and incontinence.

INVESTIGATIONS

- CT scan shows dilatation of ventricles
- X-ray skull shows large skull size in infants and young children.

MANAGEMENT

Acute deterioration

- Ventricular drainage
- Ventriculoatrial or ventriculoperitoneal shunt.
- Lumber puncture in case of communicating hydrocephalus.

Gradual deterioration

- Ventriculoperitoneal shunt.

Complications of shunt

- Infection usually with Staph. epidermidis or aureus.
- Shunt obstruction
- Subdural hematoma

NORMAL PRESSURE HYDROCEPHALUS

This term is applied when there is hydrocephalus with normal CSF pressure. It occurs usually in old age, characteristic clinical features are dementia, ataxia and incontinence. On CT scan ventricles are dilated but there is no cortical atrophy (cortical atrophy is seen in raised pressure hydrocephalus as a result of pressure of CSF on surrounding brain tissue or in Alzheimer's disease due to shrinkage of brain).

Normal pressure hydrocephalus may be idiopathic (in 50% cases) or due to preceding cause such as meningitis or subarachnoid hemorrhage. Shunting seldom helps in this condition.

HEADACHE

Arteries, venous sinus and dura mater at the base of the brain, all are sensitive to pain. Sudden distortion and displacement of these structures causes pain i.e. headache.

ETIOLOGY

Local intracranial causes

1. *Inflammation:* meningitis, encephalitis, cerebral abscess.
2. *Vascular:* Migraine, hypertension, cluster headache.
3. *Raised intracranial pressure*
4. *Reduced intracranial pressure:* due to hypotension after lumbar puncture or dehydration.

Local extracranial causes

1. Soft tissues: Boil or cellulites of scalp.
2. Referred pain from:
   - Eyes (errors of refraction, glaucoma)
   - Middle ears (otitis, mastoiditis)
   - Nose, paranasal sinus, dental pain & pain due to cervical spondylosis.

General or system causes

1. *Neuralgias:* Temporamandibular neuralgia, orbital neuralgia, trigeminal neuralgia.
2. *Metabolic factors:* Hypoglycemia, alkalosis & acidosis.
3. *Toxic factors*: Fever, uremia, drugs,
4. *Tension or psychogenic:* anxiety, mental tension & depression.

Common causes of headache

- Tension or psychogenic headache
- Fever, drug intake (e.g. nitroglycerine)
- Referred pain (e.g. errors of refraction, sinusitis)
- Vascular pain (migrain, hypertension)

MECHANISM OF HEADACHE

- Pain receptors are found in the vessels at the base of brain (both arterial and venous) and in the meninges.
- These receptors are also present in extracranial vessels, muscles of scalp, neck & face, paranasal sinuses, eye and the teeth.
- Pain receptors are not present in brain
- The headache is mediated by mechanical and chemical (serotonin, histamine) stimulation of receptors.

Special consideration

Headaches of raised intracranial pressure

- Intracranial mass lesion displaces the meninges and the basal vessels. When these structures are physically moved by changes in CSF pressure (e.g. by coughing) pain is exacerbated.
- Cerebral edema further causes displacement of structures. Headache is typically worse after lying down for some hours (as cerebral edema develops).
- Any headache present on waking which is made worse by coughing, straining or sneezing may be due to intracranial vessels dilatation and may be due to a mass.
- Vomiting often accompanies this type of headache.

Single episode of severe headache is caused by:

- Subarachnoid hemorrhage
- Migraine
- Meningitis (occasionally)

Subacute onset headache

The onset and progression of headache over days or weeks should always be suspected due to intracranial mass or serious intracranial illness e.g. encephalitis, meningitis.

Recurrent headaches are caused by

- Tension
- Migraine
- Sinusitis
- Glaucoma
- Malignant hypertension

Chronic headache recurring for several years

- Tension psychogenic
- Migraine

MANAGEMENT

1. Treatment of the cause
2. For psychogenic or tension headache.
    - Firm reassurance
    - Analgesics
    - Tranquilizers
    - Physical treatment – massage
    - Antidepressants – when depression is the cause.

MIGRAINE

Migraine is an episodic headache, which is typically unilateral and often associated with vomiting and visual disturbance.

In many patients, however the headache is bitemporal and generalized and there may be no associated focal visual or neurological disturbance. The single most characteristic feature is an episodic nature of the headache.

PATHOGENESIS

Initial vasocontriction followed by vasodilatation.

Prodromal symptoms

There is decrease in cerebral blood flow (cerebral ischemia) due to vasocontriction at the onset of an attack resulting in focal disturbance of cortical function, particularly in the occipital and parietal lobes (causing visual disturbance, nausea, tingling of limbs, transient aphasia and vague weakness of one side).

Headache phase:

During headache phase, there is vasodilatation of the extracranial & meningeal arteries, with stimulation of nerve endings (pain receptors) near affected extracranial and meningeal arteries. Fluctuation of serotonin (5-hydroxytryptamine) level in blood is thought to play a role, because it rises in prodromal phase and falls during headache.

PRECIPITATING FACTORS

1. Intake of chocolate (high in phenylethylamine)
2. Intake of cheese (high in tyramine).
3. Alcohol
4. Migraine is common around puberty, at the menopause and pre-menstrually, sometimes increases in severity with contraceptive pills or with development of hypertension.

TYPES

1. Classical
2. Common
3. Hemiplegic
4. Basilar

> **CLASSIFICATION OF MIGRAINE**
>
> **Classical migraine**
> Visual or sensory symptoms precede or accompany the headache.
>
> **Common migraine**
> No visual or sensory features
> Recurrent attacks of headaches, nausea, vomiting, and photophobia.
>
> **Hemiplegic migraine**
> Prolonged headache lasting hours or days, followed by hemiparesis which recovers slowly over days.
>
> **Basilar migraine**
> Prodromal symptoms are circumoral tingling, numbness of tongue, vertigo, diplopia, transient visual disturbance or complete blindness, syncope, dysartheria and ataxia followed by headache (usually occipital).

CLASSICAL MIGRAINE

Clinical features

Classical migraine usually starts after puberty and continues until the late middle life (mostly in women). Attacks occur at intervals, which vary from a few days to several months, and last for hours to days. The attack itself may be divided into:

- Prodromal symptoms
- Headache and associated symptoms.

__Prodromal symptoms:__

- These are usually visual in the form of zigzag lines, flashing, colored lights and defects in the visual fields.
- In some patients transient aphasia together with tingling, numbness or vague weakness of one side.
- Prodromal phase lasts for 15 minutes to 1 hour or more & is followed by headache.

__Headache and associated symptoms.__

- The headache is usually localized to the frontal region and spreads to affect the whole of one side of the head, but may become generalized (i.e. begins often locally and then becomes generalized). The pain is severe and throbbing.
- Pain is associated with vomiting, photophobia, pallor and prostration. The patient is irritable and prefers to be in a darkened room.
- After several hours the attack ceases. There is sometimes diuresis towards the end of an attack. Sleep often follows.

Differential diagnosis

Sudden onset of headache may be similar to meningitis, subarachnoid hemorrhage.
Hemiplegic migraine should be differentiated from TIA.

Management

General measures

- Reassurance and relief of anxiety
- Avoidance of precipitating factors
- Stop contraceptive pills, if attacks are frequent.

__During the attack__

1. *Aspirin* (Dispirin 300mg) 2-3 tablets OR paracetamol (Tab. Calpol 500 mg) 2 tablets. Caffeine containing analgesics such as Panadol Extra are more effective.
2. *Metochlopramide* (Maxolon) an anti-emetic with aspirin or paracetamol.
3. *Ergotamine tartrate (Migril)* 0.5-1 mg. In classical migraine relieves headache if taken as soon as visual or secondary symptoms are felt. Four tablets can be taken at half hourly interval. Ergot preparation should be avoided in pregnancy and in patients with history of vascular disease.

Side effects: Nausea, vomiting and vasospasm (paradoxically causing headache).

Contraindications: pregnancy, ischemic heart disease, and peripheral vascular disease.

4. Sumatriptan: a serotonin agonist may be given subcutaneously.
5. Zolmitriptan: another serotonin receptor antagonist, has high bioavailability after oral administration and is effective in acute attack. Dose 2.5 mg--- relief occurs within 1 hour.

Prophylaxis
Prophylactic treatment may be necessary if migranous headache occurs more than 2-3 times a month. One of the following drugs may be used. The antimigranous effect is usually seen after 2 weeks. Continue treatment for 6 months and then taper to assess the continued need for it.

- Beta-blockers: Propranolol (Inderal) 2-160 mg twice daily. Atenolol (Tenormin) may be used in dosage of 50-200 mg once daily.
- Antidepressants: Amitriptyline (Tryptanol) 10-150 mg at night. Fluxetine (Flux) may be used in the dosage of 20-60mg once daily.
- Calcium channel antagonists: Verapamil (Calan) 80-160mg, other calcium channels may be used. Flunarizine (Cap. Sibelium 5 mg) is a selective calcium antagonist and is effective for migraine prophylaxis.
- Anticonvulsants: Valporic acid (Epival) 500-1000mg twice daily. Phenytoin (Dilantin) may be used in dosage of 200-400 mg once daily.
- Pizotifin (Mosegor) Serotonin antagonist 0.5 mg at night.
- Methysergide (serotonin antagonist) 2-6 mg daily in resistant cases.

CLUSTER HEADACHE

Cluster headache or migranous neuralgia affects predominantly middle aged men causing recurrent attacks of excruciating pain that usually occur at night during sleep, awaking the patient due to pain and persists for less than 2 hours.

Episodes of severe pain around one eye occur daily for several weeks and accompanied by ipsilateral nasal congestion, rhinorrhea, lacrimation, redness of eye and Horner's syndrome.

Spontaneous remission then occurs, and patien remains well for weeks or months before anothe bout of closely spaced attacks occur.

Treatment

Acute attack
Oral therapy during attack is usually not much effective. Inhalation of 100% oxygen for 15 min or ergotamine tartrate inhaler may be effective.

Prophylaxis
Ergotamine tartrate (Migril) 2mg daily. Other drugs used as prophylactics are lithium carbonate, verapamil, and prednisolone 20-40 mg/day for 2 weeks followed by gradual tapering.

GIANT CELL ARTERITIS

Giant cell arteritis or cranial arteritis or temporal arteritis is a granulomatous arteritis of unknown etiology affecting chiefly elderly above 60 years of age.

CLINICAL FEATURES

Headache
Pain is felt over the inflamed superficial temporal or occipital arteries. Touching the skin over the inflamed vessel (e.g. combing the hair) causes pain. Arterial pulsation is soon lost and artery becomes hard, tortuous and thickened. The skin over the vessels may become red.

Facial pain
Pain in face, jaw and mouth occur due to inflammation of vessels, it is characteristically

worse on eating (*called jaw claudication*). Opening the mouth and protruding the tongue is difficult.

Visual problems

Visual loss occurs in 25% of untreated cases. Patient complains of sudden unilateral visual loss which is painless.

System features

Generalized muscle pain, proximal limb girdle pain and tenderness (i.e. polymyalgia rheumatica) occur in about 50% of cases.

Thoracic aortic aneurysms occur 17- times more frequently in patient with giant cell arteritis than in normal population.

INVESTIGATION

- ESR is greatly elevated (commonly 60-100)
- CRP (C-Reactive proteins) is raised.
- Normocytic normochromic anemia and thrombocytosis may be present.
- Biopsy of superficial temporal artery confirms the diagnosis, an adequate biopsy specimen (2 cm in length) is essential because the disease may be patchy. Unilateral temporal artery biopsy is positive in 80-85% while bilateral biopsy is positive in 90-100%.

TREATMENT

Prednisolone 60-100mg daily should be started immediately to prevent blindness even before biopsy, once blindness develops, it is usually permanent. The dose of prednisolone is maintainefd for 1-2 months before tapering and reduced gradually as the ESR falls. Headache subsides within hours of the first dose of steroid. Treatment is continued for some months to several years.

DEMENTIA

Dementia is a diffuse deterioration in brain neuronal function produced by a number of pathological processes. It is characterized by disturbance of multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning, language and judgment. However consciousness is not impaired.

Dementia affects about 19% of those aged over 65 years and 20% of over 80 years of age.

CAUSES OF DEMENTIA

Degenerative

- Alzheimer's disease
- Pick's disease
- Huntington's disease
- Parkinson's disease
- Normal pressure
- Hydrocephalus

Vascular

- Cerebrovascular disease
- Cranial arteritis

Metabolic

- Uremia, renal dialysis
- Liver failure
- Remote effects of carcinoma

Toxic

- Alcohol
- Occupational exposure
- (e.g. chemicals)
- Heavy metals (e.g. lead)

Vitamin deficiency

- B_{12}
- Thiamin

Traumatic

- Post-head injury
- Punch drunk syndrome
- (Boxers)

Intracranial space occupying lesions

- Subdural haematoma
- Tumours
- Anoxic
- Cardiac arrest
- Respiratory failure
- Carbon monoxide poisoning

Infections

- Encephalitis of any cause
- Creutzfeld-Jacob disease
- HIV infection
- Syphilis

Endocrine

- Hypothyroidism
- Hypocalcaemia

CLINICAL FEATURES

Symptoms

Decline in intellectual functions such as memory, abstract thinking, and judgment.

Signs

- Focal neurological deficits
- Involuntary movements
- Positive grasp reflex, glabellar reflex a palmomental reflex.

MANAGEMENT

- Treatment of the cause
- Symptomatic treatment.

ALZHEIMER'S DISEASE

This is the most common cause of dementia, occurring mostly in patients over 45 years. Genetic factors are important if the age of onset is under 65 years.

Pathology

- Macroscopically, the brain is atrophic, particularly the cerebral cortex and hippocampus.
- Microscopically there is neuronal reduction, presence of senile plaques, neurofibilary tangles and amyloid angiopathy in the cerebral cortex. There is disturbance in neurotransmission due to reduction in enzyme choline acetyltransferase and acetylcholine.

Clinical features

- Impaired ability to learn new information or to recall previously learned information.
- Decline in language function and increased difficulty with names and understanding what is being said.
- *Apraxia*-an impaired ability to carry out motor activities despite intact motor function.
- *Agnosia*-the failure to recognize or identify objects despite intact sensory function.
- Impairment of executive functioning such as planning organizing, sequencing abstracting.
- Behavioral changes such as agitation and aggression.
- Depression, paranoid delusions.

Investigation

- Blood CP
- Blood sugar, urea, electrolytes
- LFTs
- Serum calcium
- Serum vitamin B12
- T3, T4, TSH
- HIV antibodies
- Chest x-ray
- CT or MRI to confirm presence of cortical atrophy and to exclude other lesions such as a brain tumor.

Treatment

Try to find out the correctable cause and remove it. There is no effective treatment for Alzheimer's disease. Recently anticholinestrase drugs are approved that increase cholinergic activity in brain (since there is cholinergic deficiency in Alzheimer's disease). These drugs are tacrine, rivastigmine and galantamine. These drugs improve cognitive function in Alzheimer's disease.

MULTI - INFARCT DEMENTIA (MID)

This is the second most common cause of dementia. There is usually a history of TIAs, paresis, or visual loss. The dementia may follow a succession of acute strokes or less commonly after a single major stroke. MID results from occlusion of vessels supplying the cerebra cortex and subcortical structures and is typically associated with cortical dysfunction (focal loss of function). CT scan shows low-density areas of infarction.

MOVEMENT DISORDERS

The voluntary movement is controlled by the interaction of the pyramidal, cerebellar and extrapyramidal systems with each other as well as cranial nerve motor nuclei. The extrapyramidal system consists of nuclei of basal ganglia. Movement disorders are also called dyskinesias.

CLINICAL FEATURES

There are two types of dyskinesias:

- ***Hpokinetic movement disorders*** characterized by reduction or absent purposeful motor activity such as in Parkinsonism.
- ***Hperkinetic movement disorders*** characterized by excessive amount of spontaneous motor activity or abnormal involuntary movements Involuntary movements may be regular such as tremors or irregular such as, chorea, athetosis dystonia, ballismus and rigidity.

TREMORS

There are three types of tremors:

- Rest tremors: these tremors are maximal at rest and become less prominent with activity. Examples are Parkinsonism and drug induced caused by phenothiazines.
- Postural tremors: these tremors are maximal while limb posture is actively maintained

against gravity and lessened by rest and are not markedly enhanced during voluntary movement toward the target. Examples are hyperthyroidism, stress, toxicity and familial essential tremor.

Intention tremors: these tremors are more prominent during voluntary movement toward the target and is not present during postural maintenance or at rest. Example is cerebellar lesion.

CHOREA

Chorea consists of an involuntary, irregular, jerking movements affecting limb and axial muscle groups, they have semipurposeful appearance such as crossing and uncrossing of legs.

Causes

- Huntington's disease
- Sydenham's chorea
- Benign hereditary chorea
- Abetalipoproteinemia with chorea
- Chorea associated with:
  - Drugs – phenytoin, levodopa, alcohol
  - Thyrotoxicosis, pregnancy and oral contraceptive pill
  - Systemic lupus erythematosus
  - Polycythemia vera
  - Encephalitis lethargica
  - Stroke (basal ganglia)
  - Rarities (tumour, trauma, subdural haematoma, carbon monoxide poisoning).

Huntington's disease

Huntington's disease is an autosomal dominant disorder with onset in middle life and progression to death within 10-12 years.

There is cerebral atrophy with marked loss of small neurons in basal ganglia. Inhibitory neurotransmitters such as GABA and acetylcholine are deficient.

No treatment arrests the disease but chorea can be reduced with phenothiazines.

Sydenham's chorea

Sydenham's chorea is post-infective chorea occurring largely in children and young adults as a complication of rheumatic fever associated with streptococcal infection.

The onset of chorea is usually gradual over a few weeks. Initially there is irritability, emotional lability and then development of chorea.

Recovery occurs spontaneously within weeks or months. Benzyl penicillin is given up to the age of 20 to prevent rheumatic heart disease.

ATHETOSIS

Athetosis presents in childhood and appears as a slow writhing (twisting) movement that occurs nearly continuously in distal muscles involving digits, hands, and face.

Athetosis may result from:

- Hypoxic neonatal brain injury
- Kernicterus
- Lipid storage disease



HAMIBALLISMUS

This is a movement disoruer characterized by unilateral, violent swinging of limbs. It results from infarction or hemorrhage in the contralateral subthalmic nucleus.

MYOCLONUS

Myoclonus is a sudden involuntary jerking of a single muscle or group of muscles. Examples are benign nocturnal essential myoclonus, myoclonus in epilepsy.

TICS

Tics are repetitive jerky movements of the face, neck and trunk. They can be voluntarily suppressed. Examples are grimacing, shoulder shrugging, sniffing and throat cleaning.

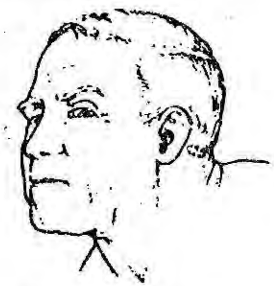
DYSTONIA

Dystonia is a sustained abnormal posture produced by contraction of large trunk and limb muscles such as sustained head retraction.

Types

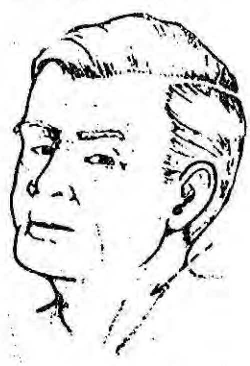
Idiopathic torsion dystonia:

Onset in childhood. Initially, a flexion deformity of leg develops when walking, and then movements become generalized with abnormal posturing of head, trunk and limbs. Cause is known. Treatment is levodopa, carbamazepine or anticholinergics.



Spasmodic torticollis

Dystonic spasm initially develops around the neck, usually in 3rd – 5th decade causing the head to turn or to be drawn backward or forward. Cause unknown. Treatment is heloperidol or anticholinergic such as benzhexol. Injection of botulinum toxin may be helpful.



NEUROLEPTIC MALIGNANT SYNDROME

Neuroleptic malignant syndrome (NMS) is a complication of neuroleptic (antipsychotic) drugs. It occurs mostly in young adults any time during the treatment, Usually within first 30 days of use in about less than 2% of patients. Exact cause is unknown but dopamine antagonism is likely contributor.

Features of NMS are:

- Lead-pipe rigidity
- Hyperthermia
- Altered mental status
- Labile blood pressure (sometimes lo sometimes high).
- Autonomic dysfunctions
- Tachypnea, tachycardia
- Metabolic acidosis

Differential diagnosis

Extrapyramidal syndrome (EPS) that is also drug induced but does not present with fever.

Complications

Renal failure, pulmonary embolism, chronic cerebellar syndrome.

Treatment

- Antipyretics
- Sponging or other ways of artificial cooling
- Rehydration
- Antispasmodics such as dantroline
- Dopaminergic agonist such as bromocriptine.

CEREBELLAR DYSFUNCTION

Cerebellum consists of two lateral lobes (hemispheres) and one central structure vermis. Each hemisphere coordinates movement of ipsilateral limb while the vermis controls axial functions such as eye movements, head and trunk posture, stance and gait.

CAUSES OF CEREBELLAR DYSFUNCTIONS	
Tumors	• Hemangioblastoma • Medulloblastoma • Secondary tumors • Acoustic neuroma
Vascular lesions	• Hemorrhage • Infarction • AV malformation
Infections	• Abscess • HIV
Developmental	• Arnold- Chiari malformation • Cerebral palsy
Toxic and metabolic	• Anticonvulsant drugs • Chronic alcohol abuse • CO poisoning • Lead poisoning
Inherited	• Friedreich's ataxia • Ataxia telangiectasia • Essential tremor
Miscellaneous	• Multiple scelrosis • Hydrocephalus • Hypothyroidism • Cerebral edema of chronic hypoxia

COMMON CAUSES OF CEREBELLAR DYSFUNCTION

- Infarction or hemorrhage
- Multiple sclerosis
- Space occupying lesion in the posterior fossa including cerebellopontine angle tumor
- Phenytoin toxicity
- Alcoholic cerebellar degeneration
- Paraneoplatic manifestation of bronchogenic carcinoma
- Hypothyroidism
- Friedreich ataxia.

CLINICAL FEATURES

LESIONS OF CEREBELLAR HEMISPHERE

A lesion within one hemisphere (e.g. a tumor or infarction) disrupts the normal sequence of movements on the side of lesion manifesting as:

Nystagmus
Coarse horizontal nystagmus appears, the direction of rapid phase is towards the side of lesion.

Ipsilateral gaze paresis
Patient is unable to move both eyes coordinately to the side of lesion.

Dysarthria
Speech is affected with bilateral lesions. A jerky dysarthria results in scanning speech.

Dysmetria
Loss of finger-nose coordination (past pointing)

Rebound phenomenon
Rebound phenomenon results from inability to arrest strong contraction on sudden removal of resistance. Patient is asked to outstretch hands, now the hands are pressed downwards by the examiner and he released, there is rebound upward overshoot of hands.

Intention tremors
Action tremors with past-pointing are seen when the finger-nose test is performed.

Dysdiadochokinesia
It is the impairment of rapid alternating movements such as supination and pronation.

Hypotonia
Absent reflexes or pendular reflexes
Tendon reflexes take pandular quality due to hypotonia, so that several oscillations of limbs may occur after the reflex is elicited (e.g. pandular knee jerk).

Ataxia
Gait becomes ataxic with a broad base; the patient tends to fall towards the side of lesion.

MIDLINE CEREBELLAR LESIONS

(Usually due to multiple sclerosis or tumors)

- **Nystagmus**
- **Head and trunk titubation:** oscillation of head and trunk.
- **Truncal ataxia:** presents as difficulty in standing and sitting unsupported.
- **Ataxic gait**

INVESTIGATION

MRI is the investigation of choice to identify cerebellar lesion.

TREATMENT

Treatment according to the cause.

DISEASE OF THE SPINAL CORD

PARAPLEGIA

Paralysis confined to the lower limbs is called paraplegia. It is an important short case very frequently asked in exams.

ETIOLOGY

DUE TO UPPER MOTOR NEURON LESION

SPINAL LESIONS (Common)

Spinal cord compression resulting from:

Vertebral (Extradural)

- Tuberculosis (Pott's disease)
- Metastatic carcinoma (from breast, lung, prostate)
- Multiple-myeloma.
- Intervertebral disc prolapse, fracture
- Cervical spondylosis

Meninges (Intradural)

- Tumors: meningioma, lymphoma, metastasis
- Epidural abscess

Spinal cord (Intramedullary)

- Spinal cord tumors

Vascular:

Hemorrhage, infarction

Systemic degeneration of tracts

- Multiple sclerosis
- Motor neuron disease
- Syringomyelia, friedreich's ataxia
- Subacute combined degeneration of spinal cord.

Infection

Acute transverse myelitis

Neurosyphilis

CEREBRAL LESIONS (uncommon)

- Thrombosis of superior sagital sinus
- Tumor of falx-cerebri
- Hydrocephalus

DUE TO LOWER MOTOR NEURON LESION

Anterior horn cells

- Poliomyelitis
- Spinal muscular atrophy
- Motor neuron disease.

Peripheral nerve
Peripheral neuropathy

Neuromuscular junction
Myasthenia gravis

Muscles
Muscular dystrophies

ACUTE PARAPLEGIA

- Epidural abscess
- Epidural spinal cord ischemia
- Transverse myelitis
- Trauma to lower back, midline disc herniation, limber intraspinal metastasis
- Guilain-Barre syndrome
- Anterior cerebral artery ischemia
- Sagital sinus thrombosis
- Cortical venous thrombosis
- Acute hydrocephalus

SUBACUTE OR CHRONIC PARAPLEGIA

- Chronic spinal cord compression
- Tuberculoma
- Multiple sclerosis
- Intramedullary tumors
- Subacute combined degeneration.

COMPARISION OF UPPER AND LOWER MOTOR NEURON LESIONS

Features	Upper motor neuron lesion (UMN)	Lower motor neuron lesion (LMN)
	UMN starts from motor cortex to the cranial nerve nuclei in brain and anterior horn cells in spinal cord	LMN is the motor pathway from anterior horn cell (or cranial nerve nucleus) via peripheral nerve to the motor end plate
Bulk of muscle	No wasting of the muscles	There is wasting of the affected muscles
Tone of muscle	Tone increases	Tone decreases
Power of muscle	Paralysis affects movements of group of muscle	Individual muscle is paralyzed
Deep tendon reflexes	Deep reflexes are exaggerated, clonus may be present	Deep reflexes are diminished or absent. No clonus
Superficial reflexes	Lost (such as abdominal reflex)	Not affected
Planters	An extensor planter response(upgoing)	Flexor response (downgoing)
Fasciculations	Absent	present

PHYSICAL EXAMINATION

Examine the patient to identify the cause and site of the lesion. Proper examination will help you a lot in finding the site and cause of paraparesis or paraplegia.

Motor system: look for: especially concentrate on

- Wasting, tone, grade of power.
- Defect in coordination (cerebellar signs)
- Fasciculations
- Reflexes
- Gait.

Sensory system: look for:

- The pattern of sensory loss
- Identify the sensory level on the trunk.
- Examine for posterior column sensations.
- Demonstrate signs of spinal cord compression with radicular (root pain).

Sphincters: examine for incontinence or retention of urine and feces.

Examination of spine: for deformity, tenderness.

Examine for associated features

- Anemia- for B_{12} deficiency
- Constitutional features suggesting tuberculosis elsewhere in the body causing Pott's disease.
- Stiff neck due to cervical spondylosis
- Per rectal examination of prostate for malignancy.
- Look for features of malignancy anywhere in the body especially breast lung, prostate, kidney, lymphoma and multiple myeloma.

INVESTIGATIONS IN PARAPLEGIA

Plain X-ray of vertebral column

Following changes on plain X-ray spine may be detected: TB spine, herniated intervertebral disc, secondary deposits, fracture or dislocation of vertebra and cervical spondylosis.

MRI

MRI is the investigation of choice for paraplegia.

Blood CP

It may detect megaloblastic anemia as a cause of subacute combined degeneration of spinal cord.

Fundoscopy

For papilloedema due to intracranial tumor or multiple sclerosis.

MANAGEMENT OF PARAPLEGIA

Skin care

- The patient should be turned every 2-4 hours to a position which avoids pressure sores on bony prominence, because pressure sores are liable to develop due to loss of sensation, diminished blood supply and immobility
- Skin should be dry & clean.
- If pressure sores develop, use "pressure ring" & antibiotics.

Bladder Care

Aseptic intermittent catheterization if urinary retention occurs.

Bowel Care

Constipation must be avoided by suitable diet & laxatives.

Prevention of contracture

Contracture of the limbs can be prevented by regular passive movements. Nursing the patient in posture that discourages flexion of the joints.

Rehabilitation

Using wheel chair & adopting a suitable occupation

DESCRIPTION OF CAUSES OF PARAPLEGIA

Now we will discuss common causes of paraplegia with some diagnostic aspects.

SPINAL CORD COMPRESSION

Spinal cord compression may be acute with trauma metastasis or arterial occlusion or it may be slow developing over weeks such as in Pott's disease, cervical spondylosis and other conditions mentioned above.

Sensory symptoms such as paraesthesia or numbness and localized pain over spine or root distribution occur early, while weakness and sphincter dysfunction are late manifestations.

SYMPTOMS OF SPINAL CORD COMPRESSION

Pain
Localized over the spine or in a root distribution which may be aggravated by coughing, sneezing or straining.

Sensory
Paraesthesia, numbness or cold sensation, especially in the lower limbs, which spread proximally, often to a level on the trunk.

Motor
Weakness, heaviness or stiffness of the limbs, most commonly the legs.

Sphincters
Urgency or hesitancy of micturition, leading eventually to urinary retention.

SIGNS OF SPINAL CORD COMPRESSION

Cervical, above C5
Upper motor neuron signs and sensory loss inall four limbs.

Cervical, C5 to T1
Lower motor neuron signs and segmental sensory loss in the arms, and upper motor neuron signs in the legs.

Thoracic cord
Spastic paraplegia with a sensory level on the trunk.

Conus medullaris
Lesions at the end of the pinal cord cause loss of sensation in the sacral area dn extensor plantar responses.

Cauda equina
The spinal cord ends at approximately the T12/L1 spinal level and spinal lesions below this level can only cause lower motor neuron signs by affecting the cauda eqina.

INVESTIGATIONS FOR CORD COMPRESSION

X-rays spine AP & lateral
Plain x-ray may show osteophytes due to degenerative process or bony destruction due to infection or tumor.

X-ray chest
It may indicate aprimary tumor or infection.

MRI of spine
It is the investigation of choice.

TREATMENT

The management and prognosis of spinal cord compressiondepends on nature of the underlying lesion.

Brief description of important lesions causing spinal cord-compression

- Spinal tuberculosis
- Spinal cord tumors
- Epidural abscess

SPINAL TUBERCULOSIS (POTT'S DISEASE)

- Spinal tuberculosis usually occurs in the absence of extraspinal tuberculosis.
- It often involves two or more adjacent vertebral bodies. Upper thoracic spine is most commonly involved in children while the *lower thoracic and upper lumber vertebrae* are usually affected in adults.
- Intervertebral disc is also destroyed. A paravertebral cold abscess may also form.
- Pain occurs over affected area and is made worse by weight bearing.
- Anterior superior or inferior angle of vertebral body is initially involved. With advanced disease, collapse of vertebral bodies results in kyphosis (called gibbus).

Investigations
X-ray spine, CT or MRI

Management

- *Immobilization:* For examination of spine do not ask the patient to sit; just role to one side.
- *Antituberculous therapy*
- *Surgery:* anterior transthoracic decompression is performed if there is cord compression.

SPINAL CORD TUMORS

In adults majority of tumors are epidural in origin, resulting from metastasis from solid tumors such as breast, lung, prostate, kidney, lymphoma and multiple myeloma.

Clinical features

These tumors cause cord compression gradually over weeks to month, with local or referred root pain and a sensory level. The pain worsens with movement, coughing or sneezing. The pain worsens with movement, coughing, or sneezing. Intramedullary tumors have very slowly progressive course over many years.

The thoracic cord is most commonly involved except metastasis from prostate and ovary that mostly involve lumber and sacral vertebrae.

Investigations

- *MRI of spinal cord* is the investigation of choice.
- *Plain x-ray* may show osteolytic lesions or vertebral collapse. However the plain x-ray fails to identify 15-20% of metastatic vertebral lesions.

Management

Radiotherapy: it is the appropriate initial treatment. *Surgical decompression:* Rapidly deteriorating neurological condition requires surgical decompression.

Treatment is effective only if administered early, when signs of cord dysfunction are absent or mild; therapy will not reverse fixed paralysis of more than 48h duration.

ACUTE EPIDURAL ABSCESS

- Acute epidural abscess tends to occur in debilitated patients having diabetes, malignancy, hepatic or renal failure and in IV drug abusers.
- Staphylococcus is the most commonagent. Usually thoracic cord is affected.
- Patient presents with fever, bilateral leg weakness, sensory level, urinary retention, very severe pain and tenderness over the involved site.
- Blood CP shows leukocytosis and positive blood culture.
- MRI confirms the site of lesion.
- *Management:* urgent decompressive laminectomy and abscess drainage combined with IV antibiotics.

CAUSES OF PARAPLEGIA OTHER THAN SPINAL CORD COMPRESSION

- Spinal cord infarction
- Spinal cord hemorrhage
- Transverse myelitis
- Syringomyelia
- Motor neuron disease
- Subacute combined degeneration of spinal cord
- Cortical sinus thrombosis

SPINAL CORD INFARCTION

Spinal cord is supplied by one anterior spinal artery and paired posterior arteries. Spinal cord infarction is associated with aortic atherosclerosis, dissecting aortic aneurysm, hypotension, vasculitis, thrombosis or cardiogenic emboli.

Anterior spinal artery syndrome

Acute infarction in the territory of anterior spinal artery produces:

- Sudden paraplegia or quadriplegia. Initially flaccid paralysis and areflexia due to spinal shock, within few days there is spastic paralysis with hypereflexia and extensor planter response.
- Loss of pain and temperature sensation up to the level of cord damage, while sparing vibration and position sense.
- Loss of sphincter control ---urinary retention
- Back pain in the area of ischemia is frequently noted.

MRI is often normal but it is required to exclude other causes of acute cord damage.
Treatment is according to the cause. Anticoagulation is usually not indicated.

Posterior spinal artery syndrome
It is rare and presents as motor weakness and loss of joint position sense.

SPINAL CORD HEMORRHAGE

Hemorrage in the spinal cord (hematomyelia) is rare. Causes are AV malformation, trauma, tumor, infection, bleeding disorders and vasculitis.
Patient presents as acute pain and signs of spinal cord damage such as paraplegia. Diagnosis is best made by MRI. Surgical intervgention is usually not useful.

TRANSVERSE MYELITIS

Transverse myelitis is an acute or subacute inflammation of spinal cord occurring after infection or recent vaccination. Many infectious agents have been implicated such as influenza, measles, varicella, mumps, EBV, CMV, and mycoplasma. Multiple sclerosis may present as transverse myelitis.

Clinical features
Patient presents with fever, back and limb pain followed by sensory loss, paraplegia and bladder disturbance evolving within hours to several days. Sharp sensory level in transverse myelitis differentiates it from Guillain-Barre syndrome that mimics the transverse myelitis.

Investigations and treatment

- MRI shows swelling of spinal cord.
- Glucocorticoids are given in the form of injection methylprednisolone followed by oral prednisolone.
- Good recovery occurs in 30% of cases.

SYRINGOMYELIA

It is a chronic progressive disorder in which cavitation develops within the spinal cord involving the spinal canal, usually in the cervical region, sometimes extending into the medulla (called *syringobulbia).*

The expanding cavity disrupts second order spinothalamic neurons, anterior horn cells, lateral corticospinal tracts. It usually spares the tracts of posterior column.

Etiology
Blockage of the exit foramina of the fourth ventricle due to congenital deformity, the most common is the herniation of cerebellar tonsils through the foramen magnum (called Arnold-Chairi malformation).
Symptom develop usually at the age of 25-40 years, more common in males.

Clinical features

- Pain in neck and shoulder
- <u>Sensory symptoms:</u> Sensory loss in upper limb (only sense of pain and temperature are lost while touch and vibration senses are preserved). Sensation loss leads to painless burns and ulcers on the hands and painless deranged joints called Charcot joints in the upper limbs.
- <u>Motor symptoms:</u> Wasting of small muscles of hands is early feature along with loss of upper limb reflexes. Weakness of legs (paraparesis) is more insidious.
- Kyphoscoliosis, pes cavus and spina bifida are common associations.
- <u>Syringobulbia</u> leads to dysarthria, palatal palsy, Horner's syndrome, nystagmus and sensory loss on the face.

Investigation
Investigation of choice is MRI

Treatment
Treatment is surgical decompression of cavity, however the results of surgery are usually disappointing and in some patients the condition continues to progress slowly over long periods.

MOTOR NEURON DISEASE (MND)

This is a progressive degenerative disorder of unknown cause in which there is degeneration of upper and lower motor neurons in the spinal cord, cranial motor neurons and pyramidal neurons in the motor cortex. Male to female ratio is 1.5:1, prevalence is about 6 in 100 000. Mean age of onset 55 years and mean survival 50% over 3 years and 28% over 5 years.

Pathology

Loss of neurons in motor cortex, cranial nerve nuclei and anterior horn cells. No evidence of inflammation.

Clinical features

There are several patterns of motor neuron disease, the division is just to recognize the disease, and they are not different in etiology or pathology. The different names are given according to the level of nervous system involvement as following:

- Pseudobulbar palsy: due to loss of fibers from motor cortex to cranial nerve nuclei (upper motor neuron disease).
- Bulbar palsy: due to loss of neurons in cranial nerve nuclei (lower motor neuron disease)
- Progressive bulbar palsy: combination of upper and lower motor neuron disease i.e. degeneration of cranial nuclei and their connections with motor cortex. These are discussed in the section of cranial nerves.
- Primary lateral sclerosis: due to degeneration of corticospinal fibers.
- Progressive muscular atrophy: due to loss of neurons in anterior horn cells.
- Amyotrophic lateral sclerosis: due to degeneration of corticospinal fibers and anterior horn cells both.

Primary lateral sclerosis

There are features of upper motor neuron disease with spasticity, brisk reflexes, extensor planter response, weakness specially of extensors in apper limbs and flexors in lower limbs.

Progressive muscular atrophy

Onset is usually with weakness of muscles of hand or forearm which slowly progresses; grip is affected or even wrist drop occurs. Although it may begin unilaterally, wasting soon follows on the opposite side. Fasciculation is a prominent feature (fasciclations are visible muscle twitches occurring spontaneously). Tendon reflexes are lost. The disease can affect muscles of foot but less often.

Amyotrophic lateral sclerosis

It is the most common presentation of motor neuron disease. Weakness of quadriceps results in difficulty in walking or dragging of one leg.

- Lower motor neuron signs: atrophy, weakness and fasciculations are most prominent in upper limbs.
- Upper motor neuron signs: spastic paraparesis, hyper-reflexia and extensor planter response in lower limbs.

N.B.

In MND there is no involvement of sensory system, bladder or ocular muscles.

PATTERNS OF INVOLVEMENT OF MND
Progressive bulbar palsy
• Early involvement of tongue, palate and pharyngeal muscles. • Dysarthria/ dysphagia • Wasting and fasciculation of tongue • May be pyramidal signs as well.
Progressive muscular atrophy
• Predominantly spinal motor neurons affected. • Weakness and wasting to distal limb muscles first. • Fasciculation in muscles. • Tendon reflexes may be absent.
Amytrophic lateral sclerosis
• Combination of distal and proximal muscle wasting and weakness, fasciculation. • Spasticity, exaggerated reflexes, extensor planters. • Bulbar and pseudobulbar palsy follow eventually • Pyramidal tract features may predominate.

CLINICAL FEATURES OF MOTOR NEURON DISEASE

Age of onset

- Usually after age 50 years
- Very uncommon before 30 years
- Males more common than females

Symptoms

- Limb muscle weakness, cramps, occasionally fasciculation
- Disturbance of speech/swallowing (dysarthria/dysphagia).

Signs

- Wasting and fasciculation of muscles
- Weakness of muscles of limbs, tongue, face and palate.
- Pyramidal tract involvement causes spasticity, exaggerated tendon reflexes, extensor plantar responses.
- External ocular muscles and sphinchers usually remain intact
- No objective sensory deficit
- No intellectual impairment in most cases.

Course

- Symptoms often begin focally in one part and spread gradually but relentlessly to become widespread.

DIFFERENTIAL DIAGNOSIS

- Hyperthyroidism and hyperparathyroidism produce muscle wasting and hyperreflexia as in MND.
- Pseudobulbar palsy may also occur due to stroke or multiple sclerosis.
- Progressive muscular atrophy may be confused with spinal muscular atrophy, limb girdle dystrophy, diabetic amyotrophy and lead neuropathy.

INVESTIGATIONS

- EMG shows chronic partial denervation with fasciculation and fibrillation.
- Nerve conduction studies are normal.
- MRI to exclude cord compression
- Thyroid and calcium studies to exclude endocrine or metabolic disease.

TREATMENT

Treatment is symptomatic such as physiotherapy, walking aids, splints and speech therapy

SUBACUTE COMBINED DEGENERATION OF THE SPINAL CORD

This syndrome of combined spinal cord and peripheral nerve damage is a sequele of vitamin B12 deficiency due to pernicious anemia or malnutrition. Deficiency of vitamin B12 causes swelling of myelin sheath followed by demyclination and astrocyte gliosis. Changes start in posterior column (that conveys vibration and position sense) then there is involvement of lateral column (that consists of pyramidal tracts).

CLINICAL FEATURES

Paraesthesias

Tingling and numbness occurs in toes and later in fingertips. Paraesthesia begins at periphery and tends to spread upwards.

Sensory loss

Senses of vibration, posture and passive movements are affected, first in lower then in upper limbs (sensations carried by posterior column). Gloves and stoking type superficial sensory loss. There is tenderness of calf muscles. Optic atrophy in about 5% cases.

Motor symptoms

Motor defect is usually limited to legs and includes weakness and ataxia that develop after sensory disturbances. Romberg's test is positive.

Reflexes

Reflexes may be lost initially (due to neuropathy) then exaggerated and extensor planters due to involvement of lateral column of spinal cord.

Sphincter disturbance

Sphincter disturbance presents as urinary retention or incontinence, impotence is early.

Mental changes

Impaired memory, irritability, confusion, mild dementia and psychosis.

DIAGNOSIS

- Blood CP: shows macrocytic anemia
- Bone marrow: shows megaloblastic bone marrow.
- Serumvitamin B12 less than 100pg/mL
- Schilling test
- Anti-intrinsic factor antibodies

MANAGEMENT

Injection vitamin B12 1000μg (Neurobion) I/M daily for 7-10 days then weekly for a month and then monthly for the whole life.

CORTICAL SINUS THROMBOSIS

Predisposing factors

Lateral or sagittal sinus thrombosis occrs as complication of:

- Pregnancy and postpartum period
- Sepsis, meningitis
- Hypercoaguable states such as polycythemia and sickle cell anemia.

Clinical features

- Raised intracranial pressure, headache, focal seizures and infarction primarily affecting the parasagittal cortex.
- Paraparesis is common.

Investigations

- CT or MRI shows hemorrhagic infarction and may show thrombus in the affected sinus.
- MR angiography makes the diagnosis.

Treatment

Anticoagulation is recommended unless hemorrhage is prominent.

PERIPHERAL NEUROPATHY

The peripheral nerve consists of axon with its anterior horn cell, and the myelin sheath which is produced by Scwann cells.

Neuropathy means a pathological process affecting a peripheral nerve or nerves due to any cause.

Pathophysiology

Three basic pathological process affect peripheral nerve fibers.

Axonal degeneration

Metabolism of axon is affected resulting in degeneration of the distal portion of axon. Axonal degeneration occrs typically in toxic neuropathies.

Demyelination

When the Schwann cell and the myelin sheath are disrupted, there is marked slowing of nerve conduction. Demyelination is a feature of Guillain-Barre syndrome and hereditary sensorimotor neuropathies.

Wallerian degeneration

It follows transection of an axon by crushing or injury, with degeneration of myelin sheath and axon distal to the site of division.

MONONEUROPATHY

The damage to a single nerve may be acute due to compression usually affecting nerves which are exposed anatomically such as common paronial nerve at the head of fibula. The damage to a single nerve may be chronic due to entrapment (as the nerve passes through relatively tight anatomical passages such as fibro-osseus tunnels (e.g. carpal tunnel).

CARPAL TUNNEL SYNDROME

It is an entrapment neuropathy caused by compression of median nerve in the carpal tunnel in middle aged women. Cause is idiopathic in most of the patients.

Precipitating factors

1. Diabetes mellitus
2. pregnancy: due to edema
3. Rheumatoid arthritis, hypothyroidism and acromegaly: due to connective tissue thickening.

Clinical features

1. Pain, numbness, tingling or an "electric shock" feeling in thumbs and fingers supplied by the median nerve, especially after using the hand or at night wakening the patient from sleep.
2. The condition is usually bilaterally.
3. Sometimes sensory loss of the radial three and half digits.
4. Weakness and wasting of abductor pollicis brevis.
5. Tinel's sign: tapping on the carpal tinnel produces pain.

Diagnosis

Diagnosis is clinical confirmed by nerve conduction velocity (NCV) that shows slowing of conduction over the wrist.

Management
1. Rest
2. Splinting at night
3. Local injection of corticosteroid
4. If pregnancy is the cause – give diuretics
5. If myxedema -- give thyroxine
6. Surgical decompression of the nerve in carpal tunnel if all above measures fail.

COMMON ENTRAPMENT NEUROPATHIES
- **Median nerve :** (carpal tunnel syndrome)
- **Ulnar nerve:** (at elbow, causing paraesthesia on medial border of hand)
- **Radial nerve :** causing wweakness of extension of wrist and fingers (usually in sleep due to abnormal posture).
- **Peroneal nerve:** causing foot drop
- **Lateral cutaneous nerve of thigh:** causing tingling on lateral border of thigh (called meralgia paraesthetica, usually in pregnancy).

MONONEURITIS MULTIPLEX
(Multiple mononeuropathy)

In mononeuritis multiplex there is involvement of more than one nerve affected in patchy distribution.

Causes
- Diabetes mellitus
- Vasculitis
- Leprosy
- Sarcoidosis
- Amyloidosis
- Malignancy
- Neurofibromatosis
- HIV infection.

Diagnosis and management
Diagnosis is usually clinical confirmed by nerve conduction studies. Treatment is that of underlying cause.

POLYNEUROPATHY

Polyneuropathy is a diffuse, symmetrical disease process involving peripheral nerves, starts affecting distal parts then progressing proximally and may be actue, subacute or chronic. Polyneuropathy may be motor, sensory, sensorimotor (i.e. mixed) or autonomic.

ACUTE POLYNEUROPATHY

GUILLAIN BARRE SYNDROME

Guillain- Barre (Gian Bari) syndrome is also known as acute inflammatory or post-infective demyelinating polyneuropathy. It develops 1-3 weeks after respiratory infection or diarrhea in more than 70% of cases. Infecting organisms are Epstein Barr virus, CMV, and campylobacter jejuni in majority of patients.
In some patients it occurs after surgery or immunization.
Age is usually 20-50 years, predominantly males.

Pathology
There is demyelination of spinal nerve roots or peripheral nerves, which is immunologically mediated.

Clinical features
- There is rapidly progressive muscle weakness, often ascending from lower to upper limbs and more marked proximally than distally (ascending paralysis). Distal paraesthesia and limb pains often precede the weakness.
- In most patients muscle weakness progresses for 1-3 weeks, but rapid deterioration with respiratory muscle paralysis can occur within hours.
- In about 20% of cases there is involvement of bulbar, facial or respiratory muscles.
- Examination shows weakness and absent reflexes, there may be sensory loss at the periphery in an ascending pattern from the fingers and toes.
- There may be features of autonomic neuropathy (hypo- or hypertension, tachy- or bradycardia).

Investigations

NCV: nerve conduction velocity shows the slowing of nerve conduction or conduction block consistent with underlying segmental demyelination.

CSF: shows raised protein (may be normal in the first 10 days). There is no rise in cell number, lymphocytosis more than 50/mm suggests an alternative diagnosis.

Course and prognosis
In the untreated case, recovery begins after 3 weeks, however during this 3 week period patient may need ventilator, therefore assessment of ventilation with vital capacity and blood gases should be done repeatedly. About 80% of patients recover completely within 3-6 months, 4% die, and remainder suffer residual neurological disability which can be severe.

Management
Nursing care, nutrition, monitoring for ventilatory functions.

Plasma pharesis (plasma exchange):
Plasma pharesis is very effective if initiated within first 2 weeks of illness. (usually 4-5 sessions are required and each session costs about 8-10 thousand rupees. For plasma pharesis in Karachi consult Bismillah Taqi Institute of Blood Diseases, NIPA chourangi Gulshan- e- Iqbal (previous Shan Hospital).

Immunoglobulin
Intravenous administration of high dose immunoglobuilin (2g/kg given over 5 days) is as effective as plasma pharesis. It is also expensive. There is no role of corticosteroids.

CHRONIC POLYNEUROPATHY

ETIOLOGY

Toxins

- Drugs: Isoniazid, ethambutol, chloroquine, metronidazole, lithium, phenytoin vincristine, amiodarone.
- Alcohol
- Heavy metals:; lead, gold, arsenic, mercury
- Organic solvents.

Vitamin deficiency
Vitamin A, B2, B6, B12, E and folic acid.

Metabolic & endocrine disorders
Diabetes, renal failure, hepatic failure, hypothyroidism and gout.

Connective tisse disorders
Rheumatoid arthritis, SLE, polyarteritis nodosa

Malignant disease
Carcinoma especially bronchogenic carcinoma, lymphoma, leukemia, multiple mycloma.

Infections
Leprosy, typhoid, tuberculosis, meningitis, acute infective polyneuritis.

Genetic
Hereditary motor and sensory neuropaty.

CLINICAL FEATURES

Sensory

- *Sbjective disturbances* – Numbness, tingling, feelings of pins and needles (paraesthesias in the feet and then later in the hands). Burning sensations and pain in the extremities.
- *Objective sensory loss* – bilateral, symmetrical impairment of all forms of sensation in a "glove and stocking" distribution. Preceding the anesthesia, there is hyperesthesia. Tenderness of calf muscles is sometimes present.

Motor

- Usually extensor are more affected than flexors, hence wrist drop or foot drop occurs.
- Atrophy of the muscle may be present.
- Tendon reflexes are absent or reduced. Ankle jerk earliest to be affected.

Autonomic
Dryness or excessive sweating of the extremities, postural hypotension, impotence,diarrhea or constipation.

Skin changes
Skin becomes glossy, furrowing and falling of nails, cold extremities.

DIAGNOSIS

History:
Especially of drug intake and potential exposure to toxin.

Investigation:
- Blood suger, urea, and electrolytes to exclude metabolic disorder.
- Nerve conduction test to confirm neuropathy
- Nerve biopsy: Sural or radial nerve palsy in neuropathy of uncertain cause.

MANAGEMENT

General measures
- Elimination of possible toxic or infectious cause
- Control of any existing metabolic or nutritional deficiencies. High protein diet & multivitamins.

Local measures
- Relief of pain: Hot packs or soaks, infra-red light and analgesics
- Prevention of foot drop and wrist drop and contracture, by splints and sand bags.
- Daily massage and passive movements.

Specific measures
- Vitamins B1 for thiamine deficiency (Neurobion).
- Corticosteroids.
- Control of metabolic disease e.g. diabetes
- Impramine is beneficialfor diabetic neuropathy in some patients.
- Immunosuppressive or cytotoxic drugs give response in some patients.

CLINICAL TYPES OF POLYNEUROPATHY

Acute neuropathy
- Guillain-baree
- Diphtheria
- Malignancy

Painful neuropathy
- Nutritional deficiencies
- Diabetic amyotrophy
- Toxic neuropathy due to metronidazole
- Hereditary sensory neuropathy.

Predominantly motor
- Gullain-Baree
- Lead posoining
- Porphyria, diphtheria
- Charcot-Marie Tooth disease

Predominantly sensory
- Diabetetes
- Vitamin B1 and B12 deficiency
- Hereditary sensory neuropathy
- Uremia
- Malignancy

DISEASES OF MUSCLES

DISORDERS OF VOLUNTARY MUSCLES
- Muscular dystrophy
- Myotonias
- Metabolic and endocrine myopathy
- Inflammatory mopathy
- Congenital myopathy
- Toxic myopathy

MUSCULAR DYSTROPHY
Progressive muscular dystrophy is a group of hereditary disorders characterized by progressive degeneration of a group of muscles without involvement of nervous system.

Clinical features
1. Symmetrical wasting and weakness
2. Tendon reflexes are preserved until late state
3. There is no sensory loss

Investigation

1. Electromyography (EMG)
2. Muscle biopsy
3. Serum creatinine phosphokinase (CPK) is markedly raised in Duchenne muscular dystrophy but normal or moderately raised in other types.

Management

No specific therapy. Physiotherapy is helpful.

Clinical types of muscular dystrophies

DUCHENNE'S MUSCULAR DYSTROPHY

Duchenne's (Dushenz) muscular dystrophy is the most common form of muscular dystrophy. It is an X-linked recessive disorder that affects predominantly males. There is deficiency of protein dystrophin in muscles. Symptoms begin by age 5 years and patient is severly disabled by adolescence, death occurs by the age 20 years.

Clinical features

- Initially the patient has difficulty in running and rising to erect position from the floor. Weakness is more marked in the proximal lower limbs. In an attempt to rise to stand from a supine position, patient characteristically must use their arms to climb up their bodies (Gower's sign).
- Pseudohypertrophy of the calves caused by fatty infiltration of muscle is common.
- Heart is involved late in the course.

Investigations

- CPK: 100-200 times raised.
- EMG: shows myopathic pattern
- Muscle biopsy: Shows fiber necrosis, regeneration and replacement by fat.

Management

There is no definitive treatment available, but some suggest that prednisolone 1.5mg/kg/d orally may improve muscle strength for the short term period (up to 6 months).

BACKER'S DYSTROPHY

This is also X-linked and weakness like Duchenne's dystrophy. Age of onset is about 11 years and death occrs at about 42 years. Dystrophin level is normal but it is qualitatively altered.

LIMB GIRDLE AND FACIOSCAPULOHUMERAL DYSTROPHY

LIMB GIRDLE AND FACIOSCAPULOHUMERAL DYSTROPHIES

	Limb girdle	Facioscapulohumeral
Inheritence	Autosomal recessive	Autosomal dominant
Onset	10-20 years	10-40 years
Muscles affected	Shoulder and pelvic girdle	Face, shoulder and pelvis
Progress	Severe disability within 20-25 years	Normal life expectancy. Slow progression
Pseudo-hypertrophy	Rare	Very rare

DISTAL MYOPATHY

Tis is autosomal dystrophy typically presents after age 40. Small muscle of hands and feet, wrist extensors and dorsiflexors of the foot are affected. The course is slowly progressive.

OCULAR DYSTROPHY

It is an autosomal dominant disorder. Onset is before 30 years.

Ptosis is the earliest manifestation; facial weakness is also common. The course is slowly progressive.

OCULOPHARYNGEAL DYSTROPHY

It is an autosomal dominant disorder. It begins in third to fifth decade. Findings include ptosis, dysphagia, external opthalmoplegia, facial weakness and often proximal limb weakness. CPK ismildkly raised.

DYSTROPHIA MYOTONICA

Myotonia means continued muscle contraction after the cessation of voluntary effort i.e. there is delay in muscle relaxation. Dystrophia myuotonica is an autosomal dominant condition characterized by

progressive distal muscle weakness, with ptosis, weakness of the face and sternomastoid along with myotonia. This disease also comprises cataract, frontal baldness, intellectual impairment, cardiomyopathy, hypogonadism, glucose intolerance and low serum 1gG. Onset is between 20 and 50 years. Phenytoin helps to reduce myotonia.

METABOLIC AND ENDOCRINE MYOPATHY

CAUSES OF METABOLIC AND ENDOCRINE MUSCLE WEAKNESS	
Acute muscle weakness	**Proximal myopathy**
Hypokalaemia	Hyperthyroidism
Hyperkalaemia	Hypothyroidism
Hypocalcaemia	Hyperparathyroidism
Hypercalcaemia	Hypoparathyroidism
	Cushing's syndrome
	Addison's disease

HYPOKALEMIA

- Acute hypokalemia (e.g. in diuretic therapy) causes a severe flaccid paralysis that is reversed by correcting the electrolyte balance.
- Chronic hypokalemia (also commonly caused by diuretics) gives rise to mild proximal weakness.

Iypokalemic periodic paralysis

- It is usually inherited as an autosomal dominant trait, and is characterized by generalized weakness (quadriparesis), including the speech and bulbar muscles that often starts after a heavy carbohydrate meal (such as in dinner party) or following a period of rest after exertion. Attacks last for several hours.
- It is often first noticed in the teenage before 20 years of age and tends to remit after the age of 35 years.
- Serum, potassium is usually below 3mmol /L, the weakness responds to administration of potassium chloride.
- Similar weakness also occurs in hypokalemia during thyrotoxicosis.

Hyperkalemic periodic paralysis

This condition is transmitted as an autosomal dominant trait, is characterized by weakness that is sometimes precipitated by exercise. Attacks start in childhood and remit after the age 20 years. Attack lasts from 30 min to 2h. serum potassium is raised. Treatment is intravenous calcium gluconate or frusemide 20-40 mg or glucose.

INFLAMMATORY MYOPATHY

Polymyositis: Described in the chapter of connective tissue.

TOXIC MYOPATHY

Some drugs can cause muscular disorders, e.g. thiazide diuretics, steroids, alcohol.

CONGENITAL MYOPATHY

This is rare and presents in infancy with muscular weakness and limpness.

NEUROMUSCULAR JUNCTION DISORDERS

MYASTHENIA GRAVIS

Myasthenia gravis is an acquired autoimmune disorder of neuromuscular junction causing skeletal muscle fatigability and weakness. Patient presents with weakness and fatigability of proximal muscles of limb, ocular and bulbar muscles. It affects individuals in all age groups, but peaks of incidence occur in women in their twenties and thirties and in men in their fifties and sixties. Over all women are more affected thanmen.

Etiology and pathogenesis

- The exact cause is unknown, 1gG antibodies to acetylcholine receptor protein are found. The basic defect is decrease in the number of available acetylcholine receptors at neuromuscular junctions due to antibody – mediated autoimmune attack.
- The antibody is produced by B-lymphocytes defectively controlled by T lymphocytes because of a disorder of the thymus gland. Thymic hyperplasia is found in 70% of myasthenic patients below the age of 40 years, in about 10% of patients a thymic tumor is found.

- Myasthenia gravis is also associated with thyroid disease, rheumatoid arthritis, pernicious anemia and SLE. It is sometimes caused by treatment with penicillamine.

Clinicalfeatures

- *Relapsing and remitting course*: Relapse may be precipitated by emotional disturbances, infections, pregnancy, aminoglycosides, magnesium sulphate enema and severe muscular effort.
- *Ocular muscle*: Weakness of lids and extraocular muscles are involved early and patient presents with diplopia and ptosis.
- *Bulbar muscles:* weakness of palate, tongue, pharynx leads to difficulty in chewing, swallowing and speaking.
- *Limb weakness:* weakness of limbs is often proximal and may be asymmetrical. Muscles of shoulder girdle are more affected, patient can not undertake work above the level of shoulder e.g, combing. *Tendon reflexes are normal.* Movement although initially strong but rapidly weakness during repeated use. Severe fatigue after vigorous exercise or towards the end of the day and improvement following rest or sleep.

  Respiratory muscles: Respiratory muscles may be involved resulting in respiratory failure.

Investigations

Tensilon test

Edrophonium (an anticholinestrase) 2 mg is given IV, if definite improvement occurs, the test is considered positive and is terminated. If there is no change, the patient is given an additional 8mg. Improvement lasts for 2-3 minutes when the test is positive.

Occasionally the test itself causes bronchial constriction, nausea, salivation, fasciculations and syncope, therefore should be performed where all resuscitation facilities are available. Atropine 0.6mg should be at hand for IV administration if the symptoms develop.

Serum acetylcholine receptor antibodies

These IgG antibodies are present in more than 90% of cases. In pure ocular myasthenia they are usually undetectable. Positive test is supportive but negative test does not rule out myasthenia gravis.

Nerve stimulation

Nerve stimulation shows decrement in the evoked muscle action potential following continued stimulation of the motor nerve.

Search for associated conditions

- Chest X-ray and CT or MRI for detection of thymoma.
- ESR is not raised, CPK normal, muscle biopsy is usually not performed.
- Tests for other autoimmune diseases such as ANA, RA factor.

DIFFERENTIAL DIAGNOSIS OF MYASTHENIA GRAVIS

Other conditions similar to myasthenia gravis that cause weakness of cranial and/or somatic muscles include:

- **Lambert-Eaten myasthenic syndrome**
- **Hyperthyroidism**
- **Botulism**
- **Intracranial mass lesion**
- **Progressive external opthalmoplegia**
- **Treatment with penicillamine**

Lambert-Eaten myasthenic syndrome

- It is a presynaptic disorder of neuromuscular junction caused by autoantibodies directed against calcium channels resulting in impaired release of acetylcholine (while myasthenia is postsynaptic receptor disorder).
- A majority of cases with this syndrome have an associated malignancy, most commonly small cell carcinoma of lung, which is thought to trigger the autoimmune response.

Lambert-Eaten syndrome causes weakness similar to myasthenia gravis. Proximal muscles of lower limbs are more commonly affected; there is ptosis and diplopia also.

This syndrome is differentiated from myasthenia gravis by the fact that in this syndrome *tendon reflexes are depressed or absent*, there are autonomic changes such as dry mouth and impotence and nerve stimulation test shows incremental response while in myasthenia gravis reflexes are normal, no autonomic changes and reduction in amplitude of evoked potential in nerve stimulation test (decremental response).

Management of myasthenia gravis

The Principles of treatment are:

1. to maximize the activity of acetylcholine at the remaining receptrs in the neuromuscular junctions with the help of anticholinesterases.
2. To limit or abolish the immunological attack on motor endplates with the help of steroids, immunosupresants, plasma pharesis or intravenous immunoglobulin.

Pyridostigmine (Tab. Mestinon 60mg) is most widely used drug that gives improvement in most of the patients. The drug prolongs the action of acetylcholine by inhibiting the action of the enzyme cholinesterase.

Dosage: 30-120mg 6 hourly, determined by the response of the patient. Onset of action within 15-30 min and duration 3-4 hours.

Side effects: diarrhea, abdominal cramps, salivation and nausea. Oral atropine with each dose helps to reduce these muscarinic symptoms.

Cholinergic crisis: overdose of anticholinesterase drugs cause depolarization block of motor end plates, with muscular fasciculations, paralysis, pallor, sweating, excessive salivation & small pupil.

Surgical removal of thymus gland produces improvement in more than 85% of patients even in the absence of thymoma. If thymoma is present it should always be removed to prevent local spread although majority of thymomas are benign. Improvement with thymectomy is typically delayed for months to years. Therefore it is the consensus that thymectomy should be carried out in all patients with generalized myasthenia gravis (not in localized to oclar muscles) between the age of puberty and 55 years and in those who have had the disease for less than 10 years.

Steroids

Corticosteroids are used when there is an incomplete response to anticholinesterases. There is improvement in 70% of cases, although this may be preceded by an initial marked exacerbation of myasthenic symptoms, therefore steroid should be started in hospital.

Prednisolone (Tab. Deltacorti 5mg) start with 15-20 mg/d increased gradually up to 50mg/d for 1-3 months then increase dose on alternate-day regimen for 1-2 months until a dose of 100mg on alternate day is reached. Patient improves within a few weeks after reaching maximum dose and this improvement continues for months or years. Dose of prednisolone is then gradually reduced.

Azathioprine, cyclosporine

Azathioprine is the most commonly used because of its safety. It is added to steroids and allows reducing the dose of steroids. Initial dose is 50mg/d to test for adverse effect, typical dose range is 2-3mg/kg/d. The beneficial effect of azathioprine takes at least 3-6 months to begin and even longer to peak.

Side effects: idiosyncratic reaction consisting of fever, malaise, bone marrow suppression or abnormalities of liver function.

Cyclosporine has more rapid effect than azathioprine. Side effects are hypertension and nephrotoxicity.

Plasma pharesis and immunoglobulin

They help in myasthenia crisis or in preparing the patient for thymectomy.

IMMUNOLOGICAL TREATMENT OF MYASTHENIA

Thymectomy

- Should be performed as soon as feasible in any patient with myasthenia not confined to extrocular muscles, unless the disease has been established for more than 7 years.

Plasma exchange

- Removing antibody from the blood may produce marked improvement but, as this is usually brief, suchtherapy is normally reserved for myasthenic crisis or for pre-operative preparation.

Intravenous immunoglobulin

- An alternative to plasma exchange in the treatment of severe myasthemia.

Corticosteroid treatment

- Improvement is commonly preceded by marked exacerbation of myasthenic symptoms and treatment should be initiated in hospital. It is usually necessary to continue treatment for months or years, often resulting in adverse effects.

Other immunosuppressant treatment

- Treatment with azathioprine 2.5 mg/kg daily is of value in reducing the dosage of steroids necessary and may allow steroids to be withdrawn. The effect of treatment onclinical disease is often delayed for several months.

UNCONSCIOUSNESS AND COMA

DEFINITIONS

- **Consciousness** means awareness of onself and the surroundings in a state of wakefulness.
- **Clouding of consciousness** is reduced wakefulness or awareness
- **Sleep** is a state of mental and physical inactivity from which the subject can be aroused.
- **Stupor** is an abnormal, sleepy state from which the patient can be aroused by stimuli that may need to be repeated or vigorously applied.
- **Confusion** is the state of altered consciousness in which patients are bewildered and misinterpret the world around them.
- **Delirium** is an abnormal state in which there is confusion and often hallucinations
- **Coma** is state of unrousable unresponsiveness.

<u>Grading of coma</u>

Grade I: Patient responds to vocal command
Grade II: Maximum response to minimum stimuli.
Grade III: Minimum response to maximum stimuli
Grade IV: No response to whatever the stimuli

ETIOLOGY

Systemic causes

- *Metabolic:* Renal failure, hepatic failure, hypo/hypernatremia, hypo/hyperkalemia, hypo/hyperglycemia, metabolic acidosis.
- *Endocrine:* Diabetic ketoacidosis, myxoedema, Addison's disease, hypopituitarism
- *Drug overdose and poisons:* Barbiturates, organophosphorus poisoning (e.g. DDT), alcohol, antidepressants, anticonvulsants.
- *Physical agents:* Hypothermia, heat stroke
- *Decreaed cardiac output*: Arrythmias, MI.

Intracranial disorders

- *Trauma*: Head injury
- *Infections:* Meningitis, encephalitis, brain abscess, and cerebral malaria.
- *Vascular:* Intracerebral hemoorhage, subarachnoid hemorrhage, cerebral infarct with edema, hypertensive encephalopathy.
- *Other:* Epilepsy.

CHOICE OF ANTIMICROBIALS

ORGANISM	FIRST CHOICE	OTHERS
Gram positive cocci		
1. Streptococcal pneumoniae (pneumococcus).	- Penicillin	- Erythromycin. - Septran. - Azithromycin. - Clarithromycin. - Cephalosporin.
2. Streptococci a) Beta-hemolytic streptococci.	- Penicillin	- Erythromycin. - Cephalosporin. - Clarithromycin.
b) Streptococcus viridans.	- Pencillin + Gentamicin	- Cephalosporin.
3. Staphylococcus a) Penicillinase-Producing	- Nafcillin.	- Vancomycin. - Augmentin. - Unasyn.
b) Non-Penicillinase producing.	- Penicillin.	- Cephalosporin. -Vancomycin.
c) Methicillin-resistant.	- Vancomycin + gentamicin.	- Septran. - Minocine.
Gram negative cocci		
1. Neisseria gonorrhea	- Rocephin. - Cefspan.	- Ciprofloxacin. - Ofloxacin.
2. Neisseria meningitides	- Penicillin	- Claforan. - Rocephin. - Cefizox. - Chloramphenicol. - Ampicillin
Gram negative bacilli		
1. E.coli (UTI)	- Septran.	- Amplicillin. - Ciprofloxalin. - Cephalosporin.
2. E.coli (sepsis)	- Claforan. - Rocephin. - Fortum. - Cefizox	- Ampicillin. - Septran. - Ciprofloxacin. - Aminoglycosides.
3. H.Influenza (Resp. Infections)	- Septran.	- Ampicillin. - Amoxicillin - clarithromycin. - Doxycycline. - Zinnat.
Klebsiella	Fortum. Rocephin.	Claforan. Rocephin. Septran.
	Claforan.	Aminoglylosides. Ciprofloxacin.
5. Proteus	Ampicillin	Piperacillin. Aminogly coside. Septran.
6. Enterobacter	Septran. Imipenem.	Ciprofloxacin. Aminoglycoside. Ciprofloxacin.
7. Campylobacte	Erythromycin	Tetracycline. Ciprofloxaccin.
8. Bacteroides	Metronidazole.	Clindamycin. Imipenem. Unasyn.
9. Pseudomonas	Aminoglycoside + Piperacillin	-Fortum + aminogly coside -Imipenem + aminoglycoside. -Aztreonam + aminoglycoside. -Ciprofloxacin + piperacillin. -Ciprofloxacin + Fortum.
10. Salmonella	Ciprofloxacin. Rocephin. Ofloxacin.	
11. Shigella	Ciprofloxacin. Tari. Ofloxacin.	
12. Serratia	Claforan. Rocephin. Fortum.	
13. Vibrio cholera	Tetracycline	Ciprofloxacin. Septran. Ofloxacin.
Gram positive bacilli		
1. Clostridium	Penicillin	Metronidazole Clindamycin. Imipenem.
2. Corynebacterium diphtheria	Erithromycine	Penicillin

INFECTIOUS DISEASES 10

Infectious diseases

CLASSIFICATION OF BACTERIA

BACTERIA

- *Aerobes*
  - **Gram Staining**
    - **Cocci**
      - **Gram positive**
        - Staphylococci
        - Streptococci
        - Pneumococci
      - **Gram negative**
        - Gonococci
        - Meningococci
    - **Bacilli**
      - **Gram positive**
        - Cornyebacterium diptheriae
        - B. Anthrax
      - **Gram negative**
        - Vibrio Cholera
        - E. Coli
        - Klebsiella
        - Proteus
        - Pseudomonas
        - Salmonella
        - Shigella
  - **Ziehl Neelsen acid fast staining.**
    - Mycobacterium tuberculosis.
    - Mycobacterium leprae
- *Anaerobes*
  - **Clostridia**
    - Cl. Welchi.
    - Cl. Tetani
    - Cl. Botulinum
    - Cl. Septicum
  - **Spirochetes**
    - Treponema Pallidum
  - **Bacteroids**

SEPSIS

The systemic inflammatory response to microbial invasion is called sepsis.

Dysfunction of major organs occurs in severe sepsis and it may lead to septic shock. Early sepsis is usually reversible, whereas patients with septic shock often die despite aggressive therapy. Septic shock complicates about 20% of bacteremias.

Definitions Often Used to Describe the Condition of Septic Patients

Term	Definition
Bacteremia (fungemia)	Presence of viable bacteria (fungi) in the blood, as evidenced by positive blood cultures
Septicemia	Systemic illness caused by the spread of microbes or their toxins via the bloodstream
Systemic inflammatory response syndrome (SIRS)*	At least 2 of the following 4 conditions: (1) oral temperature of >38°C or <36°C; (2) respiratory rate of >20 breaths/min or Pa_{CO_2} of <32 torr; (3) heart rate of >90 beats/min; (4) leukocyte count of >12,000/μL or <4,000/μL or >10% bands
Sepsis*	SIRS that has a proven or suspected microbial etiology
Severe sepsis* (similar to "sepsis syndrome")	Sepsis with one or more signs of organ dysfunction, hypoperfusion, or hypotension, such as metabolic acidosis, acute alteration in mental status, oliguria, or adult respiratory distress syndrome
Hypotension*	Systolic blood pressure <90 mmHg—or 40 mmHg less than patient's baseline blood pressure—in the absence of other reasons for hypotension
Septic shock*	Sepsis with hypotension that is unresponsive to fluid resuscitation plus organ dysfunction or perfusion abnormalities as listed above for severe sepsis
Refractory septic shock	Septic shock that lasts for >1 h and does not respond to fluid and pressor administration
Multiple-organ dysfunction syndrome (MODS)*	Dysfunction of more than one organ, requiring intervention to maintain homeostasis

* Term preferred by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference, 1992.

Organisms involved in sepsis

- Gram negative bacilli 60%
- Gram positive cocci 40%
- Fungi: much less common: particularly occurring in immunocompromised patients.

ETIOLOGY

- Sepsis can be a response to any class of microorganisms (bacteria, viruses, fungi, and parasites). Microbial invasion of blood stream is not essential for the development of sepsis, local or systemic spread of microbial signals or toxins can elicit response.
- Blood culture is positive for bacteria (or fungi) in approximately 20-40% cases of severe sepsis and 40-70% cases of septic shock. In patients whose blood cultures are negative, the etiological agent is often established by culture or microscopic examination of infected material from local site.
- In previously healthy adult the most common sources of infection are intra-abdominal or UTI and pneumonia. In intravenous drug abusers staphylococcus aureus and pseudomonas are the main causative organisms.
- In many cases of septicemia the focus of infection is not apparent. Such patients are generally elderly, undernourished or suffering from chronic disease, particularly cirrhosis and diabetes.

PREDISPOSING FACTORS

Predisposing factors for Gram-negative bacteremia

- Diabetes mellitus
- Lymphoproliferative diseases such as lymphocytic leukemia and lymphoma
- Cirrhosis of liver
- Burns
- Invasive procedures
- Neutropenia

Predisposing factors for Gram-positive bacteremia

- Intravenous drug abuse
- Burns
- Vascular catheterization
- Presence of indwelling mechanical devices.

Predisposing factors for fungemia

- Immunosuppressed patients with neutropenia
- After broad-spectrum antimicrobial therapy.

SEPTICEMIA IN PREVIOUSLY HEALTHY ADULT	
Site of origin	Usual pathogens
Skin	Staphylococcus aureus, other gram positive cocci
Urinary tract	E. coli and other gram- negative bacilli
Respiratory tract	Streptococcus pneumoniae
Gallbladder or bowel	Strept. fecalis, E. coli, other gram-negative bacilli
Pelvic organs	Neisseria gonorrhea, anaerobes

SEPTICEMIA IN HOSPITALIZED PATIENTS	
Clinical problem	Usual pathogens
Urinary catheter	E.coli, klebsiella, proteus, serratia
IV catheter	Staph. aureus, staph. epidermidis, klebsiella, pseudomonas, candida albicans.
Peritoneal catheter	Staph. epidermidis
Post- surgical wound infection	Staph. aureus, E.coli, anaerobes
Burns	Gram- positive cocci, pseudomonas, candida albicans

PATHOPHYSIOLOGY

The septic response results from microbial signals or toxins and body response in the form of formation of cytokines, prostaglandins, and activation of complement C5a.

Microbial signals

Bacterial signals initiate the release of inflammatory mediators from leukocytes and endothelial cells. The interaction of these mediators leads to "inflammatory cascade" of reactions leading to widespread endothelial damage, hypotension, refractory shock, multiorgan failure and death.

Endotoxin

Lipopolysaccharide is the most potent and best-studied gram-negative bacterial signal. It is derived from cell walls of gram- negative bacteria and is a potent trigger of the inflammatory response.

Exotoxin

Exotoxins are antigenic proteins produced by bacteria such as staphylococci, streptococci and pseudomonas. Peptoglycan, lipoteichoic acid, some enzymes and toxins also act as signals in gram-positive bacterial sepsis.

EXAMPLES OF EXOTOXIN MEDIATED DISEASES

- Diphtheria
- Botulism
- Tetanus
- Diarrhea caused by vibrio cholera, salmonella, shigella, staphylococcus and E.coli.
- Toxic shock syndrome caused by staph., strept., pseudomonas.
- Pertussis
- Scarlet fever

Body response

Microbial signals act on leukocytes, humoral mediators and vascular endothelium. For example endotoxin interacts with CD 14 on the surface of monocytes, macrophages and neutrophils and initiate release of inflammatory mediators such as tumor necrosis factor (TNF) that produces characteristic abnormalities of sepsis. Other mediators are interleukin (IL) – IB, interferon gamma, interleukin-8, prostaglandins, leukotrines and complement C5a.

The interaction of these mediators leads to endothelial damage and multiorgan failure.

CLINICAL FEATURES

The clinical features of sepsis intensify over time from mild to severe. Fever, rigors and hypotension are cardinal features of severe septicemia. Lethargy, headache, and minor change in conscious level may be preceding features. In elderly and immunocompromised patients the clinical features may be quite subtle and high index of suspicion is needed.

Clinical features of septicemia

- Fever, chills or hypothermia
- Hypotension and oliguria
- Hyperventilation
- Mental status changes
- Skin manifestations
- Focal signs that localize the site infection.
- Features of complications.

On examination

- ***BP:*** Hypotension
- ***Pulse***: tachycardia
- ***Temperature:*** fever and chills are usually present. Absence of fever is most common among neonates, elderly, and debilitated patients (especially those with hepatic or renal failure).
- ***Respiration:*** tachypnea or hyperventilation (respiratory rate > 20 breaths/min) is often an early sign.
- ***CNS:*** mental status changes such as somnolence and confusion.
- ***Renal:*** oliguria
- ***Skin:*** cellulites, pustules, bullae or hemorrhagic lesions may develop when hematogenous bacteria (or their toxins) or fungi seed the skin or underlying soft tissues. For example meningococemia presents with petechial and hemorrhagic skin lesions.

COMPLICATIONS OF SEPSIS

Respiratory complications

Acute respiratory distress syndrome (ARDS) in 20-50% of patients with sepsis, most frequent due to gram – negative organisms. ARDS is characterized by Pa02 < 50 mmHg and diffuse alveolar infiltrates on x-ray.

Septic shock

Septic shock usually develops from a severe disease in systemic vascular resistance and functional hypovolemia as a result of diffuse capillary leakage of intravasclar constituents. Cardiac output is initially normal or elevated and pulse is high volume type. At the later stage there are features of hypovolemic shock.

Renal complications

Polyuria, oliguria, azotemia, and proteinuria are frequently found. Most of the time renal failure is due to acute tubular necrosis induced by hypotension or capillary injury.

Coagulation disorders

Thrombocytopenia and disseminated intravasclar coagulation (DIC).

Gastrointestinal complications

Cholestatic jaundice, with elevated levels of serum bilirubin (mostly conjugated) and alkaline phosphatase (with little change in liver enzymes) may precede the signs of sepsis. LFTs return to normal with resolution of the infection.

Altered blood glucose

Diabetic patients with sepsis develop hyperglycemia while hypoglycemia occurs more frequently in patients with underlying liver disease.

COMPLICATIONS OF SEPSIS

- ARDS
- DIC
- Renal failure
- Shock
- Hepatic failure altered blood glucose.

INVESTIGATIONS

Blood CP

Leukocytosis is common; leukopenia may occur with severe bacteremia, in alcoholics and in elderly. Platelet count is low in 75% of cases.
Hemoglobin level should be seen that might require correction.

Blood culture

For blood culture at least 2 blood samples (10ml each) should be obtained from different venepuncture sites because gram-negative bacteremia is low grade (< 10 organisms per ml of blood). Multiple blood cultures may be necessary. Blood cultures are positive in approximately 20-40% cases of severe sepsis and 40-70% cases of septic shock. In case of negative blood culture gram staining and culture of material from the primary site of infection or from infected skin lesions may help establish the microbial etiology.

Radiology

- Chest X-ray may be normal or show underlying pneumonia or diffuse infiltrates of ARDS.
- Ultrasound may be required for detection of abdominal or pelvic infection.

Urea, creatinine and electrolytes (UCE)
UCE is required for the assessment of renal status.

LFTs

- Bilirubin is raised with alkaline phosphatase (cholestatic jaundice).
- High levels of aminotransferases if present show hypoxic liver injury due to hypotension.

Urine and sputum analysis and culture

Gram-stain and culture of available pus or body fluids.

Coagulation profile
In the presence of DIC following will be the lab findings:

- Thrombocytopenia
- Low serum fibrinogen
- Prolonged PT and may be APTT
- Elevated fibrin degradation products (FDP)
- Presence of D-dimer: it is the most sensitive fibrin degradation product, since it's cross-linking implies origin from fibrin in a clot.

Arterial blood gases (ABGs)
ABGs show hypoxia, respiratory early and metabolic acidosis later.

Blood glucose

INVESTIGATIONS IN SEPTICEMIA

1. Blood CP
2. Blood culture
3. Chest x-rays
4. Ultrasound abdomen or pelvis
5. Urea, creatinine and electrolytes, RBS
6. LFTs
7. Urine and sputum analysus and culture
8. Gram stain and culture of available pus or body fluids.
9. Coagulation profile
10. Arterial blood gases

MANAGEMENT

Management aims

- To control of infection with antimicrobial agents.
- To remove the source of infection.
- To maintain organ perfusion and tissue oxygenation with hemodynamic, respiratory and metabolic support.
- To minimize the complications.

Control of infection

- Antimicrobial chemotherapy should be initiated as soon as samples of blood and other relevant sites have been collected for culture and sensitivity.
- The choice of initial therapy is based on knowledge of the likely pathogens at specific sites of local infection.
- Initiate empirical antimicrobial therapy should be effective against both gram positive and negative organisms and anaerobes. Drugs should be given intravenously in maximum recommended dosage. When culture and sensitivity reports become available, antibiotics should be changed if necessary to target the etiological agent.
- Most patients require antimicrobial therapy for at least one week; the actual duration of treatment depends on the site of infection, adequacy of surgical drainage and the patients underlying disease.

Empirical antimicrobial therapy
Initial antimicrobial therapy (regimens) for severe sepsis with no obvious source in adults. (Dose adjustment may be required if renal failure develops).

Immunocompetent adult

- Ampicillin 30 mg/kg IV 4 hourly (or ciprofloxacin 400 mg 12 hourly) plus
- Genetamicin 1.5 mg/kg IV 8-hourly plus
- Clindamicin (Dalacin 6ml) 900mg IV 8-hourly (or metronidazole 500 mg 8-hourly).

Neutropenic patient
Ceftazidime (Fortum 1 g) 2 g IV 8-hourly. Plus Tobramycin (Nebcin 20 & 80 mg) 1.5 mg/kg IV 8-hourly.

Splenectomized patient
Benzyl penicillin 2 million units IV 4-hourly. Plus Ceftriaxone (Rocephin 1g) 2g IV 12-hourly.

HEMODYNAMIC, RESPIRATORY AND METABOLIC SUPPORT.

- **Oxygen**
- **IV fluids:** 1-2 liters normal saline over 1-2 hours to maintain systolic BP > 90 mmHg.
- **Catheterize** the patient for urine measurement. Urine output should be kept above 30 ml/hour by continuing fluid administration; frusemide (Lasix) may be used if needed.
- **Inotropic support** with dopamine in renal doses (2-4μg/min) to maintain renal perfusion. Dobutamine is used for main inotropic support.
- **Fresh frozen plasma (FFP)** and platelets are required in case of bleeding disorder (e.g. DIC).
- **Nutritional support.**

PROGNOSIS

Mortality is 25-35% in patients with severe sepsis and 45-55% in those with septic shock and > 90% in those with multiorgan failure.

ANTIBIOTIC CHEMOPROPHYLAXIS

Prophylactic use of antibiotics is indicated where the risk of infection is high or the consequences of infection are very serious.

Infection to be prevented	Antimicrobial agent
Diphtheria	Erythromycin 500 mg 6- hourly for 5 days
Meningococcal infection	Rifampicin 600 mg 12- hourly for 2 days Ciprofloxacin 500 mg as a single dose.
Whooping cough	Erythromycin 500mg 6- hourly for 7 days.
Tuberculosis	Isoniazid 300mg daily for 6 months.
Rheumatic fever	Penicillin (Penidure LA) 1.2 million units IM monthly.
Endocarditis	Amoxicillin or clindamycin see endocarditis in CVS
Tetanus	Erythromycin 500 mg 6- hourly for 7 days.
Gas gangrene	Penicillin or metronidazole
Abdominal/pelvic sepsis	Cephalosporin plus metronidazole single dose
Malaria	Mefloquine 250 mg one tablet weekly or doxycycline 100 mg daily or chloroquine 150 mg two tablets weekly

SOURCES AND SPREAD OF INFECTION

Contact 1. Person to person 2. Water (skin penetration) 3. Soil (via wound)	1. Staph/strept, scabies, wound infection, infectious mononucleosis, sexually transmitted disease. 2. Tetanus, hookworm 3. Schistosomiasis, leptospirosis
Air – borne (via resp)	Measles, rubella, chickenpox, whooping cough, scarlet fever, mumps, meningococci, tuberculosis, influenza, legionella
Fecal- oral (fecal contamination of food)	Salmonella, bacillary and amoebic dysentery, cholera, giardiasis, hepatitis A, E.coli, toxoplasmosis
Transplacental	Rubella, CMV, toxoplasmosis, syphilis, malaria, HIV
Medical and nursing procedures	Hepatitis B, staph aureus, pseudomonas, tuberculosis.
Zoonoses (animal to human) 1. Beef 2. Poultry or eggs 3. Milk 4. Cheese 5. Rat's or dog's urine 6. Dog's feces 7. Dog bite 8. Birds 9. Fish	 1. Toxoplasmosis, tapeworm 2. Salmonella, E.coli, campylobacter 3. Tuberculosis, brucellosis 4. Listeriosis, brucellosis 5. Leptospirosis 6. Toxocara, hydatid cyst, toxoplasma. 7. Rabies. 8. Psittacosis 9. Tapeworm, mycobacterial infection.

VACCINES AND TOXOIDS		
Live attenuated	**Inactivated**	**Toxoid (inactivated toxin)**
Childhood immunization		
Measles Mumps Rubella Poliomyelitis BCG MMR	Pertussis H. influenzae meningococcal	Diphtheria Tetanus
Travel		
Typhoid Yellow fever	Typhoid Cholera Rabies Hepatitis A	
Special risk group		
Influenza Varicella	Pneumococcal Hepatitis B Influenza Meningococcal Plague Poliomyelitis	

PYREXIA OF UNKNOWN ORIGIN (PUO)

PUO is defined as a temperature of 101°F or above persisting or recurring during a period of 3 weeks which includes 7 day's investigations in hospital and there is failure to reach a diagnosis.
The intervals specified are arbitrary intended to exclude patients with self-limited viral illness and to allow time for the usual radiographic, serological and cultural studies to be performed.

Because of concerns over cost of hospitalization and the availability of most of the screening tests on outpatient basis, the criterion requiring 7 days hospitalization has been modified to accept patients who remain undiagnosed after 3 outpatient visits or 3 days hospitalization.

Nosocomial PUO
Nosocomial PUO is defined as a temperature of 101°F or above developing in several occasions in a hospitalized patient who is receiving acute care and in whom infection was not manifesting or incubating on admission.

Neutropenic PUO
Neutropenic PUO is a temperature of 101oF or more on several occasions in patient whose neutrophil count is < 500/μL.

HIV associated PUO
It is defined as a temperature of 101°F or more on several occasions over a period of more than 4 weeks for outpatients or more than 3 days for hospitalized patients with HIV infection.

CAUSES OF PUO

Most cases of PUO present with unusual manifestation of common rather than rare diseases.

Infections 30%

Systemic infections

- Tuberculosis
- Endocarditis
- Viral infections such as EBV and CMV.
- Toxoplasmosis
- Brucellosis
- Salmonellosis
- Typhoid
- Malaria
- HIV
- Fungal infections

Localized infections

- Liver abscess, subphrenic abscess
- Cholangitis, cholecystitis
- UTI, prostate abscess
- Sinusitis, dental abscess
- Renal or perinephric abscess
- Osteomyelitis

Malignancy 20%

- Lymphoma (both Hodgkin's and non-Hodgkin's)
- Leukemia, multiple myeloma

- Solid tumors (renal, liver, colon, stomach, pancreas.
- Renal cell carcinoma

Connective tissue diseases 15%

- Adult's still disease
- SLE
- Polyarteritis nodosa
- Giant cell arteritis
- Polymyalgia rheumatica
- Rheumatoid arthritis
- Rheumatic fever

Miscellaneous 20%

- Atrial myxoma (benign tumor)
- Hyperthyroidism, thyroiditis
- Inflammatory bowel disease.
- Cirrhosis of liver, granulomatous hepatitis
- Sarcoidosis
- Whipple's disease
- Drug fever (especially with beta-lactum antibiotics)
- Factitious fever (self-induced)

Undiagnosed 15%

Prolonged fever more than 6 months

The cause of PUO changes dramatically in patients who have been febrile for a prolonged period of time i.e. 6 months or longer. Infection, neoplasm and autoimmune diseases combined account for only 20% of cases. In these patients granulomatous hepatitis, Crohn's disease, ulcerative colitis, and factitious fever become important causes.

APPROACH TO DIAGNOSIS OF PUO

Document the presence of fever, if present then pattern of fever and its associated findings such as tachycardia and chills.

History

Thorough history of patients including

- Family history
- Occupational history
- Sexual history
- Dietary history (use of un-pasteurized products).
  Exposure to animals or chemicals.

Physical examination

Detailed and repeated physical examination, you may get some new findings if examine the patient daily.

Investigations

Lab investigations

- Routine investigations such as CP/ESR, urinalysis, RBS, urea, creatinine, electrolytes, LFTs, HBsAg, anti-HCV antibodies.
- Blood smear for malaria
- Blood culture
- Culture of urine, sputum, stool, and CSF.
- ANA to rule out autoimmune or connective tissue disease.
- MT.

Radiology

- Chest X-ray
- Ultrasound abdomen for hepatobiliary tract, kidneys, spleen, and pelvis.
- Echocardiography for evaluation of bacterial endocarditis, pericarditis, atrial myoxma.
- CT scan of chest, abdomen and pelvis.
- Upper GI barium study with small bowel follow through and barium enema.

Biopsy

Biopsy of liver and bone marrow should be considered routine in the workup of PUO if studies mentioned above are unrevealing or if fever is prolonged. Liver biopsy should be done even results of LFTs are normal. Lymph node biopsy may be helpful if nodes are enlarged.

Other measures

Flexible colonoscopy may be valuable, since colon carcinoma easily escapes detection by ultrasound and CT scan.

MANAGEMENT

- Continuous observation and examination.
- If patient is seriously ill or rapidly deteriorating empirical therapy is often given The regimen usually combines a aminoglycoside, with an anti-pseudomonas antibiotic e.g. ceftizidime (Fortum). Vancomycin should be added to the regimen if IV catheter associated infection is suspected.

- Every patient with PUO should undergo a suspected, a therapeutic trial of ATT should be given, continue the treatment for up to 6 weeks. A failure of the fever to respond over this period suggests an alternative diagnosis.
- The response of rheumatic fever and Still's disease to aspirin and NSAIDs may be dramatic. The effects of glucocorticoids on temporal arteritis, polymyalgia rheumatica, and granulomatous hepatitis are also dramatic but the empirical use of glucocorticoids should be avoided; as these agents can suppress fever if given in high enough dose, and they can also exacerbate many infections.

BACTERIAL INFECTIONS

In this section we will discuss common and important diseases. These diseases are given in sequence of:

- Gram positive cocci
- Gram negative cocci
- Gram positive bacilli
- Gram negative bacilli
- Anaerobes
- Spirochetes
- Mycobacteria

GRAM - POSITIVE COCCI

Streptococci, staphylococci

STREPTOCOCCAL INFECTIONS

Following are the clinical conditions caused by streptococci. It is very important to remember causative agent of infection; therefore proper antibiotic may be selected.

Types of streptococci

1. Group A (beta- hemolytic) streptococci e.g. streptococcus pyogenes.
2. Group B streptococci
3. Streptococcus fecalis (Enterococci)
4. Streptococcal viridans
5. Streptococcal pneumonie (Pneumococci)

Streptococcus pyogenes

- Pharyngitis
- Skin and soft tissue infection (including erysipelas and impetigo)
- Bone and joint infection
- Scarlet fever
- Glomerulonephritis
- Rheumatic fever

Group B streptococci

Neonatal infections

Streptococcus fecalis (Enterococci)

- Endocarditis
- Urinary tract infection
- Wound infection

Viridans streptococci

Endocarditis

Anaerobic streptococci

- Peritonitis
- Dental infections
- Liver abscess

Streptococcus pneumoniae (pneumococci)

- Pneumonia
- Meningitis

Group A (streptococcus pyogenes infections

PHARYNGITIS/TONSILLITIS

Presentation

Sudden onset of fever, sore throat, pain on swallowing.

On examination

- Pharynx, soft palate and tonsils are red and edematous.
- Cervical lymphadenopathy.

Complications

- *Suppurative:* Sinusitis, otitis media, mastoiditis, peritonsillar abscess.
- *Non- suppurative:* Rheumatic fever, glomerulonephritis.

Treatment

- Penicillins: amoxicillin, Augmantin.
- Macrolides: erythromycin 500mg 6- hourly or azithromycin 500 mg once daily for 3 days.

SCARLET FEVER

- Scarlet fever is common in school age children.
- It occurs 2-4 days following streptococcal pharyngitis and is caused by a specific erythrogenic exotoxin produced by streptococci.
- Fever, rigor, headache, vomiting and regional lymphadenopathy are present.
- *The characteristic feature* of scarlet fever is ***rash***, that initially occurs on the neck (behind ears) but rapidly becomes punctate (red and generalized resembling dots or sunburn). Rash is more marked in the groin and axillas (most intense in the flexures of arms & legs) and is typically absent from face, palms and soles. Rash blenches on pressure.
- Rash usually lasts for 5 days and is followed by extensive desquamation of skin.
- The face is flushed with characteristic circumoral pallor.
- Tongue has a white coating through which prominent bright red papillae can be seen *(strawberry tongue).*
- Patient is infective for 10-21 days after onset of rash unless treated with penicillin.
- Diagnosis is clinical plus throat swab culture that shows streptococcus pyogenes.
- Treatment is penicillin or macrolides.

STREPTOCOCCAL SKIN INFECTIONS

Impetigo

Impetigo is a focal, vesicular, pustular lesion with a thick amber- colored crust that has a "stuck-on" appearance.

Erysipelas

Erysipelas is a painful superficial cellulitis that frequently involves the face and is well demarcated from surrounding normal skin.

Treatment

Amoxicillin, Augmantin, first generation cephalosporin such as cephalexin, clindamycin or vancomycin.

Other infections caused by group A streptococci

- Arthritis
- Pneumonia
- Endocarditis (strept. viridans)
- *Streptococcal toxic shock syndrome:* characterized by invasion of skin or soft tissues, acute respiratory distress syndrome and renal failure. Penicillin is the drug of first choice.

Non- Group A (group B, C, G)

In non- group A streptococcal infections; Group B streptococci cause sepsis, bactremia and meningitis in neonates.

Enterococcal infections

Enterococci cause wound infection, UTI and endocarditis. Treatment penicillin, ampicillin or vancymycin.

STREPTOCOCCAL PNEUMONIAE (PNEUMOCOCCAL INFECTIONS)

Streptococcal pneumonie causes lobar pneumonia, pneumococcal endocarditis, arthritis, sinusitis.

STAPHYLOCOCCAL INFECTIONS

- Staphylococcus aureus
- Staphylococcus epidermidis

Skin and soft tissue infections

- Furuncle (boils), styes, carbuncles, abscess, cellulites and bullous impetigo.
- Scalded skin syndrome in children and toxic shock syndrome in adults.

Bone and joint infections

Osteomyelitis

Septic arthritis

Respiratory tract infections

Pneumonia

Lung abscess

Empyema

Intestinal infections

Enterocolitis

Cardiac infections

Endocarditis

Pericarditis

CNS infections
Meningitis
Brain abscess

Blood stream infections
Septicemia
Pyemic abscess

MANAGEMENT
- 90% of S. aureus strains are now resistant to penicillin & should be used only if organism sensitivity is known.
- Cloxacillin (Orbenin), erythromycin, cephalexin, clindamycin or vancomycin can be used before sensitivity report, if the disease is severe.

GRAM - NEGATIVE COCCI

Neisseria gonorrhea, bordetella pertussis
Neisseria meningitides, moroxilla catarrhalis

N. gonorrhea and bordetella pertussis are discussed here while N. meningitides in the chapter of CNS.

GONOCOCCAL INFECTIONS

Gonorrhea is caused by Neisseria gonorrhea, a gram negative diplococcus typically found inside the polymorphonuclear cells, most commonly transmitted during sexual activity.

PRESENTATIONS OF GONORRHEA

Urethritis and cervicitis

In men:

- Initially there is burning on urination and serous or milky discharge.
- One to three days later urethral pain is more pronounced and the discharge becomes yellow, creamy, profuse and sometimes blood- tinged.
- The disorder may progress to involve prostate, epididymis, and perurethral glands with acute painful inflammation.
- The disorder may regress and become chronic causing prostatitis and urethral stricture.

In women:

- Gonococcal infection often becomes symptomatic during menses.
- Women may have dysuria, increased urinary frequency and urgency with a purulent urethral discharge. Vaginitis, cervicitis with inflammation of Bartholin's glands are common.
- The disease may progress to involve uterus and fallopian tubes with acute and then chronic salpingitis resulting in scarring of tubes and sterility.
- In chronic inflammatory disease anaerobes and chlamydiae often accompany gonococci.

Investigations

- *Gram stain of urethral discharge* in men especially during the first week after onset typically shows gram – negative diplococci in polymorphonuclear leukocytes.
- Gram- stain is less often positive in women.
- Culture and sensitivity: it is the gold standard for diagnosis particularly when gram –stain is negative.
- Ligase chain reaction (LCR): in cervical and urethral swab and urine provides more rapid diagnosis of gonococcal infection with sensitivity 90-95% and specificity > 99%.

Disseminated disease

- *Gonococcal bactremia:* manifests as intermittent fever, arthralgia, and skin lesion which may be maculopapular, pustular or hemorrhagic. Skin lesions are few in number and peripherally located such as on legs.
- *Gonococcal endocarditis or meningitis* may occur but rarely.
- *Arthritis and tenosynovitis* are common, particularly involving knees, ankles, and wrists.

Conjunctivitis

Conjunctivitis is due to autoinoculation of gonococci into conjunctival sac by the person with genital infection. The purulent conjunctivitis may lead to panophthalmitis and loss of eye unless treated promptly.

TREATMENT

Urethritis and cervicitis
One of the following antibiotics against gonococci plus treatment of chlamydia because it is usually coexistent.

For gonococcal infection
One of the following drugs:

- Ceftriaxone (Inj. Rocephin 125 mg) IM single dose.
- Cefixime (Cap. Cefspan 400 mg) orally as a single dose.
- Ciprofloxacin (Tab. Ciproxin 500mg) orally as a single dose.

For chlamydial infection

1. Doxycycline (Cap. Vibramycin 100 mg) twice daily for 7 days. OR
2. Azithromycin (Cap. Azomax 250 mg) 1g orally as a single dose.

Treatment of complications

1. Salpingitis, prostatitis, bactremia, arthritis and other complications should be treated with one of the following drugs:
   - Benzyl penicillin 10 million units IV daily for 5 days.
   - Ceftriaxone 1g IV daily for 5 days.
   - Ciprofloxacin (Ciproxin 500mg) twice daily for 5 days.
2. Pelvic inflammatory disease requires clindamycin plus gentamicin.
3. Endocarditis requires ceftriaxone 1g twice daily for 3 weeks.

WHOOPING COUGH (Bordetella pertussis infection)

- Organism: Bordetella pertussis
- Spread: By droplet infection
- Age incidence: In children under 5 years (90%)

CLINICAL FEATURES

Catarrhal Stage: consists of highly infectious upper respiratory catarrh lasting about one week during which conjunctivitis, rhinitis and unproductive cough are present.

Paroxysmal Stage: Characterized by severe bouts of coughing, more severe at night. Each paroxysm consists of a succession of short sharp cough, ending in a deep inspiration during which the characteristic whoop may be heard. (It may be absent in older children & adults). The last paroxysm of a series frequently ends with vomiting. This stage lasts for one to several weeks.

Convalescene stage cough becomes less frequent & sputum less tenacious.

COMPLICATIONS

Respiratory

- Bronchopneumonia
- Atelectasis
- Bronchiectasis

Other

- Convulsions
- Conjunctival hemorrhage
- Prolapse of rectum

INVESTIGATIONS

- Blood CP: WBC count is 15000-20000/μL, 60-80% of which are lymphocytes.
- Diagnosis is established by isolating organism from nasopharynx swab culture

MANAGEMENT

1. Erythromycin 500 mg 6- hourly for 10 days.
2. Clarithromycin or azithromycin may be used.
3. Cough suppressants e.g. methadone
4. Maintenance of nutrition

PREVENTION

- DPT vaccination for infants.
- Erythromycin for prophylaxis in children and adults

MORAXELLA CATARRHALIS

This gram negative coccus causes sinusitis, bronchitis and pneumonia.

It is beta- lactamase producing and therefore ampicillin or amoxicillin are not effective.

It is susceptible to Augmantin, Septran, ciprofloxacin, second and third generation cephalosporins.

GRAM POSITIVE BACILLI

- Corynebacterium diphtheriae (causing diphtheria)
- Bacillus anthracis (causing anthrax)
- Bacillus cereus
- Listeria monocytogenes

DIPHTHERIA

Diphtheria is an acute infection caused by corynebacterium diphtheriae that usually attacks respiratory tract but may involve any mucus membrane or skin wound.

- Spread by respiratory secretions.
- Age: although it is considered as a disease of childhood but it increasingly affecting adults due to non- immunization in childhood.
- Local manifestations are due to membrane while the systemic manifestations are due to formation of exotoxin. However the presence of membrane is not essential for diagnosis. Exotoxin produced by the organism is responsible for myocarditis and neuropathy.

CLINICAL FEATURES

Nasal diphtheria

It is characterized by the presence of a unilateral, serosanguineous nasal discharge that crusts around the external nares.

Pharyngeal diphtheria

It is the most common type of diphtheria and is associated with the greatest toxicity. It is characterized by marked tonsillar and pharyngeal inflammation and the presence of membrane. This tough grayish yellow membrane is formed by fibrin, bacteria, epithelial cells, mononuclear cells and polymorph and is firmly adherent to the underlying tissue. Regional lymph nodes are enlarged and tender producing so –called "*bull-neck*".

Laryngeal diphtheria

Laryngeal diphtheria causes husky voice, brassy cough and later dyspnea and cyanosis due to respiratory obstruction.

Myocarditis

Myocarditis develops often weeks later in patients with pharyngeal or laryngeal diphtheria.

Neurological manifestations

- Palatal and pharyngeal wall palsy.
- Cranial nerve palsies, paraesthesia, polyneuropathy or rarely encephalitis.

Cutenous diphtheria

It is usually associated with burns and in poor personal hygiene.

DIAGNOSIS

Diagnosis is clinical but can be confirmed by culture of the organism.

DIFFERENTIAL DIAGNOSIS

- Streptococcal pharyngitis
- Infectious mononucleosis
- Vincent's angina
- Candidiasis

PREVENTION

1. DPT in childhood.
2. Adult type toxoid (Td) in adults.

TREATMENT

1. **Complete isolation** of patient, bed rest.
2. **Anti-txin** prepared from horse serum for all cases when diphtheria is suspected. It must be given early because to prevent further fixation of toxin to tissue receptors, since fixed toxin is not neutralized by anti-toxin.
3. **Removal of membrane** by direct laryngoscoppy or bronchoscopy may be necessary to prevent or alleviate airway obstruction.
4. **Antibiotics**

- Erythromycin 500 mg 6- hourly for 14 days. Clarithromycin or azithromycin may be used.

Prophylactic treatment

Contacts to the case should receive erythromycin 500 mg 6- hourly for 7 days to eradicate carriage.

ANTHRAX

This rare disease got public attention when used in bioterrorism against Americans when deliberately letters were contaminated with spores of Bacillus anthracis and people died due to inhalational anthrax.

Naturally occurring anthrax is a disease of sheeps, horses, goats and cattles. Spores are the infectious form of the organism. These are transmitted to human from contaminated animals, animal products or soil by inhalation or rarely by ingestion of spores resulting in cutaneous, inhalational or gastrointestinal forms of anthrax. The organism is capable of toxin production.

TYPES

Cutaneous anthrax

It is the most common form of anthrax. The small, erythematous, maculopapular lesion is initially painless that may subsequently vesiculate and ulcerate with formation of central black eschar. The illness is self- limiting in majority of cases.

Respiratory anthrax

It is also called *woolsorter's disease* and follows inhalation of spores (also in bio-terrorism). A febrile illness is accompanied by non- productive cough and retrosternal discomfort, pleural effusions are common. Mortality in untreated patient is about 90%.

Gastrointestinal anthrax

It is due to ingestion of contaminated meat. It presents as severe gastroenteritis, hematemasis and bloodly diarrhea. Toxemia, shock and death may follow.

DIAGNOSIS

The diagnosis is established by isolation of organism from culture of the skin lesion, blood or pleural fluid or CSF in case of meningitis.

Chest x-ray in inhalational anthrax shows widening of mediastinum due to hemorrhagic lymphadenitis. Pulmonary infiltrates and pleural effusion are also common.

TREATMENT

Ciprofloxacin is the drug of choice, doxycycline is an alternative first line drug.

LISTEROSIS

Listeria monocytogenes is a gram positive bacillus, usually sporadic but may spread after taking contaminated food especially dairy products.

It causes five types of infections

1. Infection during pregnancy – relatively benign disease and may resolve without therapy.
2. Neonatal infection acquired in utero, with high mortality rate.
3. Bacteremia in neonates or immunocompromised adults.
4. Meningitis in infants under 2 months and in immunocompromised adults as in AIDS.
5. Focal infections such as abscess, endocarditis, osteomylitis and arthritis.

Treatment

Drug of choice is ampicillin..

GRAM NEGATIVE BACILLI

E.coli, klebsiella, proteus, pseudomonas, H. influenzae, legionella, salmonella, shigella, campylobacter jejuni, helicobacter pylori, vibrio cholera, brucella.

These are the common infections given everywhere, we will discuss here only cholera, brucellosis and salmonella infection (typhoid fever).

CHOLERA

Cholera is a severe acute gastrointestinal infection, caused by vibrio cholera.

Transmission: by food or water contaminated by feces from a patient or carrier. Spread may occur from case to case through direct contact with feces or vomitus. It occurs mostly in hot humid season.

PATHOLOGY

Vibrio cholerae multiply in the lumen of the small bowel and are non-invasive. They secrete a powerful exotexin (enterotoxin) which activates adenylyl cyclase in intestinal epithelial cells of the

small intestine producing hypersecretion of water and chloride causing massive diarrhea of up to 15 liters per day. Severe dehydration follows rapidly. It may lead to acidosis (due to loss of alkaline fluid) and depeletion of sodium and potassium.

CLINICAL FEATURES

Stage of evacuation: Sudden onset with:

- Frequent loose motions without pain or colic, initially yellow soon become colorless watery typical "rice-water stools" which consist of clear fluid with flecks of mucus.
- Copious watery vomiting follows the diarrhoea.

Stage of collapse: The enormous loss of fluid and electrolytes lead to intense dehydration with:

- Muscular cramps due to electrolyte depletion
- Cold, clammy and wrinkled skin.
- Sunken eyes
- B.P. falls
- Pulse not palpable
- Urine output diminished.

Death may occur within few hours from circulatory shock unless fluid and electrolytes are replaced. Acidosis due to bicarbonate loss in stool & acute renal failure due to dehydration may be the complications.

DIAGNOSIS

- Diagnosis is usually clinical.
- Presence of rapidly motile vibrios in fresh stool by dark- field illumination is diagnostic (slide under microscope).
- Culture of stool or rectal swabs should be taken..

MANAGEMENT

Replacement of fluid & electrolytes:
ORS in mild cases while Ringer lactate 2-3 liters in first hour followed by normal saline one litre/hour until the pulse and blood pressure return. Once the patient is hydrated, vomiting stops and now fluid should be given orally every hour.

Drugs

- Ciprofloxacin (Novidat) infusion IV twice daily is now used preferably.
- Tetracycline I/V 6 hourly for 24 hours then 500mg orally 6 hourly for next two days may be alternative.

PREVENTION

Immunization: Vaccination for vibrio cholera provides protection for short period and is not effective in managing outbreaks of cholera.
Chemoprophylaxis with tetracycline is effective.

BRUCELLOSIS

Brucellosis is also called undulant fever or Malta fever. It is a zoonotic disease caused by Brucella, organisms enter the body through mouth, respiratory tract, genital tract or abradrd skin. Spread is usually from ingestion of raw milk from infected cattle or goats.
The bacilli travel in the lymphatics and infect lymph nodes, followed by hematogenous spread with ultimate localization of reticuloendothelial system.
Incubation period is 1-3 weeks.

CLINICAL FEATRES

Onset
Acute with high continuous fever or insidious with fever undulating over 7-10 day periods.

Symptoms
Fever, sweating, weakness, headache, anorexia, pain in limbs and back, rigors, joint pains.

Signs.
Fever
Lymphadenopathy
Hepatosplenomegaly
Spinal tenderness

COMPLICATIONS

- Relapse within 2 years of recovery
- **Localised disease** causing suppurative or granulomatous lesions including arthritis spondylitis, bursitis, osteomyelitis, meningoencephalitisd, endocarditis, epididymo-orchitis, pneumonia, hepatitis
- **Chronic brucellosis:** low-grade fever and neuropsychiatric symptoms.

INVESTIGATIONS

1. Blood & bone marrow culture are positive in 50% patients in acute illness.
2. Four –fold or greater rise in brucella antibody titer over a period of 4 weeks is highly suggestive of brucellosis.

MANAGEMENT

A combination of doxycycline 200 mg daily and rifampicin 600-900 mg daily for 6 weeks.

ENTERIC FEVER (TYPHOID FEVER)

Enteric fever is a clinical syndrome characterized by constitutional and gastrointestinal symptoms and by headache. Typhoid is the typical form of enteric fever and is caused by salmonella typhi while a similar but less severe illness known as paratyphoid is due to infection with salmonella paratyphi A, B, or C.

ETIOLOGY:

- **Transmission:** Oro-faecal route, through the contaminated food, milk or water; House flies are important vectors of infections.
- **Source of infection**: Infected excreta of the carrier individual.

PATHOLOGY

After a few days of bactraemia, the bacilli localize mainly in the lymphoid tissues of small intestine. The typical lesion is in the peyer's patches and follicles (particularly within 60 cm of ileocecal valve). These Peyer's patches become inflamed at first, then ulcerate & ultimately heal, but during the sequence they may perforate or bleed.

CLINICAL FEATURES

Invasion (1st week)

- Onset: may be insidious, with headache, bodyache, malaise, sore throat and anorexia.
- GIT symptoms:
  Tongue coated with raw tips and edges (typhoid V tongue).
  Often constipation in adults but diarrhoea & vomiting are prominent in children.
- Fever: Step-ladder fever (low in the morning but gradually increase and high in the night). Fever is usually high grade (103°F-104°F). this step- ladder pattern persists for 4-5 days and then it reaches a plateau.
- Bronchitis: Signs of bronchitis (e.g. cough) is common
- Pulse: Relative bradycardia (i.e. pulse is slower than would be expected from the height of temperature). In other fevers each degree °F rise in temperature increases pulse rate to 10/min.

3. **Advance (2nd week):**
   In untreated cases the disease progresses as following:

- Temperature – high
- Abdomen: Spleen becomes palpable at the end of 1st week and is soft & tender. Now constipation is replaced by diarrhoea and abdominal distension with tenderness in right iliac fossa.
- Rash: Rose-spot rashes appear on the upper abdomen and back in crops, slightly raised and fade on pressure.

3. Decline (3rd week)

- Mild case – toxaemia abates, gradual fall of temperature.
- Severe case: Increased toxaemia, intestinal hemorrhage & perforation. Patient may pass into coma & die.

4. **Convalescence:**
   In a typical uncomplicated case fever subsides in four weeks. There is return of appetite, tongue clears & pulse becomes faster.

Relapse may occur after 10 days of the primary attack, especially in those who are inadequately treated.

COMPLICATIONS

Intestine

- Hemorrhage: shock with blood in stool.
- Perforation: abdominal pain and tenderness, most likely to occur in the third week.

Septicaemic foci

- Cholecystitis
- Osteomylitis, arthritis
- Meningitis
- Toxic phenomenon
- Myocarditis
- Pneumonia
- Nephritis
- Thrombophlebitis

Other

- Urinary retention
- Enteric encephalopathy (psychosis).

INVESTIGATIONS

1. **WBC count:** Relative leucopenia.
2. **Blood culture**: is the most important diagnostic test for typhoid. Blood culture is positive in about 80% of patients in the first week of illness, it decline thereafter and about 25% patients have positive blood culture in the third week of illness.
3. **Bone marrow culture** may be positive when blood culture is negative.
4. **Stool cultre:** positive from 2nd week onwards.
5. **Typhidot test:** This test identifies antibodies against salmonella typhi. IgM antibodies indicate recent infection while IgG indicate remote infection.
6. **Widal test:** It is an agglutination test which detects antibodies to the causative organism. It is positive by 10th day, but maximum during 18-23rd day.
   Enteric fever stimulates both H and O agglutinins, rise in only H agglutinin can occur in any febrile illness while a rising titre of O agglutinin is evidence of active typhoid disease. Widal test is less reliable and now rarely performed in standard medical practice.
   Negative widal test does not exclude typhoid fever.

Paratyphoid fever

The course of the disease tends to be shorter and milder than that of typhoid fever bu the onset is often more abrupt with acute enteritis. The rash may be more abundant and the intestinal complications less frequent.

MANAGEMENT

General measures

- *Nursing:* Bed rest, preferably in isolation, mouth wash, skin care.
- *Diet:* Maintenance of nutrition and fluid intake especially milk.

Specific (antibiotics)

One of the following antibiotics

- Ciprofloxacin (Ciproxin) 750mg twice daily.
- Ceftriaxone (Inj. Rocephin 1g) 2g IV once daily.
- Co-trimoxazole (Septran DS) (B.D.

Duration of treatment is 14 days but 5-10 days treatment may be sufficient. Fever may persist for upto 5 days after the start of antibiotics.

Hyperpyrexia:

Tepid sponging

Treatment of carrier state

- Ciprofloxacin 750 mg twice daily for 4 weeks.
- Cholecystectomy may be required.

Prevention

Vaccination of household contacts of a typhoid carrier.

ANAEROBIC BACTERIA

Anaerobic cocci

- Peptococci
- Peptostreptococci

Anaerobic bacilli

- Clostridium perfringes
- Clostridium difficile
- Bacteroids
- Fusobacterium

GAS GANGRENE

Gas gangrene is myonecrosis caused by deep tissue infection with clostridium spp., mainly by clostridium perfringes and follows contaminated penetrating injuries. Toxin produced under anaerobic conditions results in shock, hemolysis and myonecrosis.

It is particularly associated with battlefield wounds, but is also seen in *IV drug abusers, and following surgery.* The initial infection develops in an area of necrotic tissue caused by the original injury; toxin secreted by the bacteria kill surrounding tissue and enable the anaerobic organism to spread rapidly. Toxins are also responsible for the systemic features of gas gangrene.

Clinical features

Systemic features: Onset is rapid with pain in the affected area, fall in blood pressure, tachycardia and fever. In late stages stupor, delirium and coma occurs.

Local features: The wound become swollen and surrounding skin is pale. There is foul smelling brown, blood tinged serous discharge. As the disease advances the surrounding structures become deeply coloured with fluid filled vesicles. Gas may be palpable in the tissues.

Investigations

- Diagnosis is clinical.
- X- ray shows gas within the soft tissues.
- Anaerobic culture confirms the diagnosis.

Treatment

- *Benzyl penicillin* 2 million units 3- hourly is the drug of choice. Clindamycin, metronidazole, tetracycline may be the alternatives.
- *Surgical debridement* of necrotic tissue and exposure of infected areas.
- *Hyperbaric oxygen therapy* is also used.

TETANUS

Tetanus is caused by a powerful neurotoxin (tetanospasmin) produced by strains of clostridium tetani when introduced into the tissues. The disease is characterized by muscular rigidity and spasms.

PATHOGENESIS

Infections: spores of clostridium tetani are present in feces of herbivorous animals and men and therefore also found in soil. Any kind of damage to skin or mucous membrane may cause entrance of spores to underlying tissue. In circumstances unfavourable to the growth of the organisms, spores may remain dormant for years in soil. Spores germinate and bacilli multiply only in anaerobic conditions which occur in areas of tissue necrosis. The bacteria release an exotoxin with an affinity for motor nerve endings and motor nerve cells. The involvement of anterior horn cells results in rigidity and convulsions.

PREDISPOSING FACTORS

Wounds most likely to endanger tetanus are those:

- the wounds for which treatment is delayed more than about 6 hours
- Deep or contaminated wound with soil, metal, wood, calcium salts or bacteria.
- Wound complicated by necrosis of muscles.

ROUTERS OF INFECTIONS

- Punctured or war wound
- Unsterile surgery – including use of infected catgut and swabs, criminal abortion
- Bowel surgery
- Burns
- Animal bite
- Nsterile division of the umbilical cord.
- Compound fracture.

Incubation period

6 – 10 days

CLINICAL FEATURES

Prodromal symptoms

Non specific such as fever, headache & irritability

Presenting symptoms

- Trismus: It is the spasm of the masseter muscles which causes difficulty in opening the mouth and in masticating (hence the name *"lock jaw")*
- The rigidity spreads to involve the muscles of face, neck and trunk therefore producing pain & stiffness in the neck and back.

Symptoms of established disease

Rigidity: affecting the erector spinae and abdominal muscles producing exaggerated lumbar lordosis, neck retraction and abdominal rigidity.

Muscle spasm

- *Spasm of facial muscles*: typical facial appearance with raised eyebrows, tightly closed eyes and drawing back of the lips to expose clenched teeth (risus sardonicus)

  Stimuli such as loud sounds, injections, movements and attempted nasogastric intubation may induce muscular spasm.

- Spasms of erector spinae muscles increases spinal extension and producing arching of the back (opisthotonos)
- Spasm of pharyngeal muscles causes dysphagia
- Spasm of laryngeal muscles may lead to respiratory arrest.

DIFFERENTIAL DIAGNOSIS

- **Rables**-Dysphagia associated with spasms of inspiratory and pharyngeal muscles also occurs inrabies but there is no trismus. Relaxation of muscles occr in between paroxysms.

- **Tetany**-Spasms start in peripher with carpopedal spasm. Usually associated with thyroid surgery.

- **Other causes of muscle spasms** – e.g. dystonic reactions to drugs such as phenothiazine and metoclopramide (maxolon). Rarely due to strychnine poisoning. Muscle tone returns to normal between spasms.

- **Hysterical** – Trismus without generalized rigidity; or hysterical opisthotonos which develops without pre-existing rigidity.

COMPLICATIONS

1. **Respiratory** – Bronchopneumonia is a common cause of death, resulting from aspiration of stomach contents, blockage of airways by sticky secretions and by the lung collapse.
2. **Due to spasms** – Spasm can tear muscles and even avulse their insertions, with subsequent articular and periosteal calcification and myositis ossificans. Wedge fracture of thoracic vertebrae can also result from spasms.
3. **Miscellaneous** – Hyper-pyrexia, fluid and electrolyte disturbances, especially dehydration which may contribute to the risk of deep vein thrombosis and pulmonary embolism; paralytic ileus, development of a catabolic state.

TREATMENT OF TETANUS

Neutralize absorbed toxin

Human tetanus antitoxin 3000 i.u intravenously.

Prevent further toxin production

- Debridement of wound
- Benzylpenicillin 600 mg 6-hrly i.v. (metronidazole if allergic to penicillin)

Control spasms

- Nurse in a quiet room
- Avoid unnecessary stimuli
- Diazepam IV– if spasms continue paralyse patient and ventilate

General measures

- Maintain hydration and nutrition
- Treat secondary infections.

PREVENTION

Active immunization

Tetanus toxide is administered as two doses 4-6 weeks apart, with a third dose 6-12 months later. Booster doses are given every 10 years.

Passive immunization

Passive immunization should be used in nonimmunized person and whenever a wound is contaminated or likely to have devitalized tissue. (When the risk of tetanus is judged to be present) Tetanus immune globulin 250 units given IM. Active immunization is started concurrently with tetanus toxide (Tetavax).

Destruction of spores

Destruction of spores in operation theatres by filtered ventilation and by use of antiseptics on floors and walls. Irradiation or autoclaving of surgical instruments and dressings. Povidine-iodine for skin decontamination.

Treatment of wounds

Thorough cleaning, removal of foreign material and debridement of necrotic tissue, use of an timicrobials.

The immediate danger of tetanus can be greatly reduced by the injection of 1200mg penicillin followed by a 7-day course of oral penicillin.

BOTULISM

Botulism is a paralytic disease caused by botulinum toxin produced by Clostridium botulinum that is anaerobic bacillus found in soil. The organism may contaminate many foodstuffs (canned food, preserved vegetables, contaminated honey).

Anaerobic conditions are necessary for the growth of organism. Ingestion of this potent toxin causes bulbar and ocular palsies.

Ocular palsies: presenting as diplopia, loss of accommodation, ptosis, cranial nerve palsies and fixed dilated pupils.
Bulbar palsy: presenting as dysphagia and dysphonia.
Patient remains consciousness and temperature is normal. Respiratory paralysis may lead to death unless mechanical ventilation is provided.

Investigations
Identification of toxin in food and patient's serum.

Treatment
- Botulinum anti- toxin.
- Intravenous fluids if swallowing is difficult.
- Mechanical ventilation for respiratory paralysis.

SPIROCHETAL INFECTIONS

SYPHILIS

Syphilis is a chronic systemic disease caused by Trepnema pallidum transmitted either by close sexual contact or can be transmitted transplacentlly.

CLINICAL STAGES OF SYPHILIS

Primary syphilis

Between 10 and 90 days (mean 21 days) after exposure to the pathogen a papule develops at the site of inoculation. This ulcerates to become a painless, firm chancre. This is usually accompanied by painless regional lymphadenopathy. Healing occurs spontaneously within 2-3 weeks.

PRIMARY SYPHILIS
- Painless genital ulcer (hard chancre)
- Regional lymphadenopathy

Investigations
- Darkfield microscopy shows treponemes in at least 95% of chancers.
- Rising titer of antibodies.

Treatment
- Benzathine penicillin G 2.4 million units IM in gluteal region is given once.
- Doxycycline 100mg twice daily for 2 weeks in penicillin allergic patient.

Secondary syphilis

Between 4 and 10 weeks after the appearance of the primary lesion—constitutional symptoms develop with fever, sore throat, malaise, and arthralgia. Patient may develop hepatitis, nephritis, arthritis and meningitis. Untreated early syphilis in pregnant women leads to fetal infection in at least 70% of cases and may result in stillbirth in up to 30%.

<u>On examination</u>
- There is generalized lymphadenopathy.
- Generalized skin rashes involving the whole body including palms and soles but excluding face.
- Condylomata lata: watery, plaque- like lesions found in the perianal area and other moist body sites.
- Acute neurological signs in the less than 10% of cases (e.g aseptic meningitis, cranial nerve palsies).

SECONDARY SYPHILIS
- Constitutional symptoms
- Diffuse skin rash, condylomata lata
- CNS: aseptic meningitis, cranial nerve palsy.
- Liver: hepatitis – jaundice
- Renal: nephrotic syndrome.
- Bone: periostitis

Investigations
- All serological tests for syphilis are positive.
- Cutaneous and mucus membrane lesions often show treponema pallidum on darkfield microscopic examination.

- Transient CSF pleocytosis is seen in 30-70% of cases.
- There may be evidence of hepatitis or nephritis.

Treatment
Same as given in primary syphilis if thre is no CNS involvement.

Late (tertiary syphilis)
This stage may occur ant time after secondary syphilis, even after years of latency and is seen in about 1/3 of untreated patients. It is characterized by:

Localized gummatous lesion: this is the granulomatous lesion that may occur anywhere in skin. Gummas may be found in skull, tibia, fibula and clavicle, liver and testes.
Diffuse inflammation: mainly involving CNS and large arteries. Aortic aneurysm, aortic regurgitation, or aortitis may occur. Neurosyphilis may present as subacute meningitis, intracranial mass, paraparesis, Tabes dorsalis, or general paralysis of insane.

Treatment
Benzyl penicillin 3-4 million units 4- hourly for 10-14 days.

MYCOBACTERIAL INFECTION

LEPROSY

Leprosy is a chronic granulomatous disease caused by Myobacterium leprae, (an acid-fast bacillus).

Spread: by droplets from sneeze of lepromatous patient whose nasal mucosa is heavily infected.

PATHOLOGY
The organism shows predilection for peripheral nerves, skin & mucosa of upper respiratory tract. The early infection is usually transient and self-healing, called indeterminate. If the infection does not heal, it develops into one of the determinate types – tuberculoid, lepromatous or borderline. Lepromatous and borderline lepromatus are termed as multibacillary disease.
While tuberculoid and borderline tuberculoid are termed as paucibacillary disease.

CLINICAL FEATURES

1. Tuberculoid leprosy
The onset is gradual, first symptom is a small but persistent area of impaired sensation or numbness, in some patients hypopigmentation and erythematous macules may be the first symptoms.

Nerve lesions: Sensory and or motor symptoms develop depending on the type of nerve involved. Following nerves are particularly affected.
- Great auricular nerve in the enck
- Ulnar nerve above the medial condyle
- Radial nerve at the wrist
- Median nerve at the carpal tunnel
- Superficial personeal nerve
- Posterior tibial nerve.

Skin lesions: Early manifestation is macules occurring particularly over the lateral aspect of the arms, legs, buttocks and shoulders. They have well defined edges, are hypopigmented and usually there is loss of sensation especially to light touch.
Skin is dry & scaly, anhydrosis is characteristic of skin lesions.

2. Lepromatous Leprosy
It usually commences with the appearance of macules on the skin. They are numerous, hypopigmented and erythematous. They differ from tuberculoid macules in that they are small, numerous, widely scattered on the body, usually symmetrical and margins merge imperceptibly with normal skin. Overlying sensation is not impaired.

3. Borderline leprosy
This is a mixture of lepromatous & tuberculoid. Nerve involvement is often manifested before skin lesions. The eyes & nose are not involved.

DIAGNOSIS
Multibacillary disease (lepromatouse or borderline lepromatous)
It is diagnosed by demonstration of M. leprae in material obtained by a slit skin smear.

Paucibacillary disease (tuberculoid and border line tuberculoid):
Bacilli are difficult to detect & diagnosis is usually clinical.

MANAGEMENT

Multibacillary disease: Combination of 3 drugs
- Rifampicin 600 mg daily for 4 weeks
- Dapsone 50-100 mg daily for the whole life
- Clofazimine 100mg 3 times a week for one year.

Paucibacillary
Dapsone 25-50mg daily for 3-10 years.

PARASITIC INFECTION

AMOEBIC DYSENTERY

ETIOLOGY:
Entamoeba istolytica

PATHOLOGY
- Cysts of E. histolytica are ingested in water or uncooked food which has been contamined by human feces.
- In the colon trophozoite forms emerge from the cysts, invading the mucus membrane of the large bowel. Cecum is maximally affected, but any part of colon may be affected, producing flask shaped ulcers.
- Sometime a localized granuloma (amoeboma) may present as a palpable mass in the rectum.

CLINICAL FEATRES
Intestinal amebiasis may have several presentations as following:

1. **Mild to moderate colitis (Non-dysenteric colitis)**
   It is characterized by a few stools per day that are semiformed and have no blood:
   There may be abdominal cramps, flatulence, fatigue, weight loss ; fever is uncommon. During remission patient may have constipation.

2. **Severe colitis (Dysenteric colitis)**
   - It is characterized by increased number of stools that changes from semiformed to liquid with streaks of blood. Frequency of stools increases to 10-20 or more with little fecal material but blood and bits of necrotic tissue become increasingly evident.
   - Patient may have high grade fever, colic, tenesemus, vomiting, generalized abdominal tenderness or along the line of colon, more marked over the cecum and pelvic colon..
   - Localized ulcerative lesion of colon
   - Ulceration may be limited to the rectal area.

3. **Ameboma**
   Ameboma is a localized granulomatous lesion of colon that presents as a mass. Clinical features such as pain, obstructive symptoms and hemorrhage and x- ray findings mimic colonic carcinoma or tuberculosis.

4. **Localized ulcerative lesion of colon**
   Bowel ulcerations limited to the rectal area may result in passage of formed stools with bloody exudates.

5. **Chronic amoebic dysentery:**
   It is characterized by repeated attacks of loose stools with little blood and mucus, alternating with periods of constipation. There are slight pain & definite tenderness in the abdomen usually in the right iliac fossa.

6. **Asymptomatic**
   In most infected persons, the organism lives as a commensal and the carrier is without symptoms.

INVESTIGATIONS
- *Stool D/R:* Examination of stool under microscope demonstrates motile amoeboid trophozoites.
- *Identification of amebic antigen* in stool is more sensitive and specific than microscopy.
- *Colonoscopy:* The bowel should not be cleansed by laxative or enema as this washes exudates from ulcer and destroys trophozoites.

TREATMENT

Asymptomatic intestinal infection
Diloxanide furoate (available in the combination of metronidazole by the name of Entamizole).

Nondysenteric (mild to moderate) disease
Metronidazole plus diloxanide furoate (Tab. Entamizole DS) 3-times daily for 5 days. Alternatively tinidazole may be used instead of metronidazole (Tab. Fasigyn 500mg) 4 tab. Stat then 2 daily for for 5 days.

Dysenteric (severe) colitis
- Fluid and electrolyte therapy
- Initially IV therapy with metronidazole (Flagyl) then oral treatment with Tab. Entamizole.

Macroscopy	Amoebic	Bacillary
Number	6-8 motions/day	over 10 motions/day
Amount	copious	Small
Odour	Offensive	Odorless
Color	dark red	bright red
Nature	blood & mucus mixed with feces.	blood & mucus - no feces.
Microscopic		
R.B.C.	in clumps	discrete
Pus cells	scanty	numerous
Macrophages	very few	Numerous
Eosinophils	Present	rare
parasite	E. histolytic	Nil

GIARDIASIS

Etiology

Infection with Giardia lambia (a protozoa) is common in tropical countries. They attach to the mucosa of the duodenum and jejunum and produce inflammation and partial villous atrophy.

Clinical features

1. Recurrent attacks of urgent diarrhea with abdominal discomfort and explosive loose pale stools.
2. Lethargy, flatulence, abdominal distension, epigastric pain and nausea are common.
3. It may cause severe malabsorption by producing villous atrophy.

Diagnosis

1. Stool D/Reactants: cysts are found in stool
2. Jejunal juice exâmination: Obtained during endoscopy demonstrates the giardia in jejunal juice.

Management

- Tinidazole (Fasygen) single dose 40mg/kg (range 0.5g – 2g) repeated after one week.
- Metronidazole 200-400 mg T.D.S for 14 days (but less effective).

MALARIA

It is a protozoal disease characterized by paroxysms of chills, fever and invasion of red blood cells by the parasite "plasmodium".

ETIOLOGY]

There are four species of plasmodium (malarial parasite)

1. Plasmodium vivax
2. Plasmodium malarie
3. Plasmodium ovale
4. Plasmodium falciparum

Plasmodium vivax is the most common while plasmodium falciparum is the most dangerous.

LIFE CYCLE (IN HUMAN)

Definite host: Mosquito
Intermediate host: man

1. **Sporozoltes** in saliva of female anopheles mosquito → injected in man blood by mosquito bite → invade liver cells where they grow and multiply (in this stage they do not attack R.B.C. and after injection firstly enter the liver, therefore this stage is called pre-erythrocytic stage) → the infected liver cells (called Schizont) rupture and release merozoites into the blood.
2. Merozoltes invade R.B.C. and there grow and multiply (Erythrocytic stage) → R.B.C. rupture → release of merozoites → some merozoites invade other R.B.C. while some differentiate into Gametocyte → gametocyte are sucked by anopheles.

CYCLE IN MOSQUITO

Gametocyte → Zygote → Ookinete → Oocyst → Sporozoite → Sporozoite in saliva → injection in main and then cycle is repeated.

CLINICAL FEATURES

Acute attack

Onset: Anorexia, headache, chilliness & fever

Paroxysm: malarial paroxysm can be divided into three clinical stages.

1. **Cold stage:** The patient fees intense cold, he shivers from head to foot, his teeth chatter and he covers himself with blankets. This stage lasts for 30 minutes to 1 hour. The temperature rises rapidly to as high as 41°C.
2. **Hot stage** shivering stops and patient feels intense heat, he throw off the blankets.
3. **Sweating stage** patient breaks into profuse perspiration, temperature rapidly declines with feeling of relief.

P. Vivax and P. ovale infections

- The paroxysm is repeated 48 hours later.
- Spleen & liver enlarge gradually & may become tender (in untreated cases)
- Anemia develops slowly

P. malariae infection

This is associated with mild symptoms & paroxysm is repeated every third day. It tends to run a more chronic course (i.e. to chronic malaria)

P. Falciparum Infection (pernicious malaria)

This is more dangerous than other forms of malaria.

Onset: is insidious with malaise, headache, vomiting cough & mild diarrhea.

Fever pattern is not specific. The cold, hot and sweating stages are not found.

Organ damage: Infected RBCs develop knob-like surface projections that facilitate adhesion of these RBCs to the endothelium of blood vessels. The consequent vascular occlusion causes anoxia & severe organ damage, chiefly kidneys, liver, brain & GIT.

- Splenomegaly occurs late
- Anemia develops rapidly

Clinical forms of falciparum malaria

1. Cerebral malaria is characterized by a marked elevation in body temperature headache, a rapid deterioration in consciousness, convulsions, coma and death.
2. Algid malaria: is characterized by the presence of severe vomiting, diarrhea and peripheral circulatory collapse.
3. Septicaemic malaria results in a high, continuous fever, vomiting and signs and symptoms mimicking typhoid fever. The hepatorenal syndrome & spontaneous splenic rupture may also occur.
4. Blackwater fever it is called so because of the production of dark brown-black urine owing to intravascular hemolysis, seen only in falciparum malaria. It can be precipitated by very abrupt onset of fever, marked hemolysis, hemoglobinuria, vomiting, circulating collapse and acute renal failure.

COMPLICATIONS OF FALCIPARUM MALARIA

CNS

Cerebral malaria (coma, convulsions)

Renal

- Hemoglobinuria (black water fever)
- Oliguria
- Acute renal failure

Blood

- Severe hemolytic anemia
- DIC
- Respiratory
- ARDS

Metabolic

- Hypoglycemia
- Metabolic acidosis

Gastrointestinal /liver

- Diarrhea
- Jaundice
- Splenic rupture

Other

- Shock- hypotension
- Hyperpyrexia

DIAGNOSIS OF MALARIA

Malarial parasite (MP)

Diagnosis of malaria is made by identifying parasites on Giemsa- stained thick or thin blood film. As the parasitemia is episodic, MP may be negative at some time and positive at another time. Therefore blood should be examined 8- hourly for 3 days during and between febrile spikes.

The number of red cell infected seldom exceeds 2% of total cells. In severe falciparum parasitemia infected cells may be more than 30%.

TREATMENT OF MALARIA

General

1. Analgesics and antipyretics such as paracetamol
2. I/V fluid for dehydration – if needed.

Treatment of acute attack

Chloroquine sensitive malaria

Plasmodium vivax, ovale, malariae are usually sensitive to chloroquine and this is the drug of choice.

Chloroquine (Tab. Resochin containing 250 mg chloroquine phosphate while chloroquine base is 150 mg) given as following:

- 4 tablets stat
- 2 tablets after 6 hours
- 1 tab twice daily for next two days. (Total 10 tablets course).

Following successful treatment it is necessary to give 2-3 week course of primaquine (15 mg/day) to eradicate hepatic hypnozoites and prevent relapse.

Amodiaquine (Basoquin) may be used if chloroquine is not tolerated.

Chloroquine resistant malaria

Falciparum malaria is usually resistant to chloroquine and should be treated with other drugs as following:

1. **Artemether (Artem cap. 40mg, Inj. 80 mg)**
   Inj. Artem 2 stat in gluteal area, then one daily for 4 days. OR
   Capsule: Artem 2 capsules daily for 7 days.
2. **Quinine sulphate** 600mg T.D.S. for 5 days by mouth followed by a single dose of 3 Tab Fansidar (sulfadoxine 1.5g + Pyrimethamine 75 mg)
   Quinidine can be used if quinine is not tolerated.
3. **Mefloquine (Fancimef)**
   20 mg/ kg in 2 doses 8 hours apart.
4. **Fansidar**
   3 tablets stat.
5. **Halfantrine (Halfan)**
   2 tablets 6 hourly (total 6 tablets)

> **Treatment of falciparum malaria**
> - Quinine 10mg/kg 12 hourly by I/V infusion until the patient can take drug orally.
> - I/V fluids to prevent collapse.
> - Blood transfusion with packed cell in severe anaemia
> - If oliguria develops – mannitol infusion.

TROPICAL SPLENOMEGALY SYNDROME

Tropical splenomegaly syndrome is seen in areas where malaria is hyperendemic. It is seen in older children and adults mostly females.

It is associated with an exaggerated immune response to repeated malarial infection and is characterized by anemia, massive splenomegaly, and marked elevation in serum 1gM antibodies (due to exaggerated immunoglobulin response to malaria).

- Malarial parasites are usually absent in peripheral film
- Management of tropical splenomegaly syndrome is proguanil 100mg daily for years with folic acid 5mg daily.

FILARIASIS

ETIOLOGY
Wuchereria bancrofti (filariae) is conveyed to man by the bites of infected mosquitoes. The adult worms live in the lymphatics. The female worms produce microfilaria which at night circulate in large numbers in the peripheral blood.

PATHOLOGY
- The presence of adult worms in the lymphatics causes allergic lymphangitis.
- Recurrent episodes of lymphangitis may lead to intermittent lymphatic obstruction and transient lymphoedema, which may later become permanent in the leg, arm, genitalia or breast.
- Obstructed lymphatics become dilated and tortuous and may rapture. Rupture into tissue leads to cellulites, fibrosis and elephantiasis. Increased lymphatic pressure may cause retrograde flow or rupture, in turn causing chyluria, chylous ascites or chylous pleural effusions.

CLINICAL FEATURES

1. Early inflammatory phase (lymphangitis)
There are bouts of fever accompanies by pain, tenderness and erythema along the course of inflamed lymphatic vessels. Most common affected lymphatics are of spermatic cord, epididymis & testes. Further attacks follow, temporary edema becomes more persistent and regional lymph nodes enlarge. Lymphadenitis mostly affects inguinal lymph nodes.

2. Late obstructive phase
Following repeated inflammatory reactions signs of lymphatic obstruction appear e.g. scrotum massively enlarge, chylous ascites, pleural effusion.

Elephantiasis: This is massive lymphoedema distal to blockage, one or both legs and scrotum are most commonly involved, but arms and breast may be affected. Skin and subcutaneous tissues become thickened & fissured. Eventually the adult worms may die but the lymphatics remain obstructed.

DIAGNOSIS
1. Clinical diagnosis & eosinophilia in early stage.
2. Microfilaria appear in the blood at night after about a year from the time of infection and can be seen moving in a wet blood film made at midnight. When the elephantiasis develops, microfilaria become difficult to find.

MANAGEMENT

Diethylcarbamazine (Hetrazan 50mg) 1 tablet T.D.S. for 3-4 days then 3-4 tablets TDS for 2 weeks.
Side effects: Temporary exacerbation of symptoms may occur in the beginning of treatment as a result of toxic proteins released from dead organisms.
The treatment should not be stopped; corticosteroids and antihistamine can relieve this allergic reaction.
Other side effects are dizziness, nausea, vomiting & rash.

Plastic surgery: for re-establishment of lymphatic drainage.
Crepe bandage, elastic stockings and raising the affected part may control the swelling to some extent.
In advanced cases surgical removal of elephantoid tissue followed by extensive skin grafting to restore the mobility of the patient may be advised.

SCABIES

Organism: Sarcoptes scabei – a mite (arthroped)

Clinical features
Itching: Initially between the fingers, on the buttocks or genitals where the mite burrows, and later all over the body.

Management
1. Permethrin (Lotrix cream) single application to the whole body below the neck.
2. Benzyl benzoate 15% - 3 days applications.

MEASLES

- Organism: paramyxovirus
- Age incidence: Mostly children between ages of 3-5 years.
- Spread: Droplet infection & direct control.

CLINICAL FEATURES

1. Prodromal phase usually lasts for 4-5 days

- *Catarrh* (common cold) presenting with nasal catarrh, sneezing, redness of conjunctivae, watering of the eye & photophobia.
- *Fever:* abrupt rise of temperature to about 102°F.
- *Koplik's spots:* They are diagnostic of measles, appear on 2nd day and fade after 3-4 days. These are small whitish spots surrounded by a narrow zone of inflammation occurring on buccal mucosa usually opposite lower molars.
- *Laryngeal involvement:* Hoarseness & cough due to laryngitis
- *Gastrointestinal*: Vomiting & diarrhea.

2. Stage of Eruption

Rash: On 5th day red macules appear first at the back of ears and at the junction of the forehead and the hair. Within a few hours there is invasion of the whole skin. As the spots rapidly become more numerous they fuse to form the characteristic blotchy appearance of measles. When the rash is fully erupted, usually in 2-3 days, it tends to deepen in color and then fades into a faint brown staining followed by fine desquamation.

COMPLICATIONS

Effects of measles virus

- Stomatitis
- Enteritis
- Pneumonia
- Keratitis

Secondary bacterial infection

- Otitis media
- Bronchopneumonia
- Conjunctivitis

Neurological complications

- Post-viral encephalitis
- Sub-acute sclerosing panencephalitis

Nutritional

- Severe weight loss
- Kwashiorkor (tropics)
- Corneal ulceration

MANAGEMENT

- Isolation – Child should not go to school for 10 days.
- Bed rest – in quiet shaded room during febrile period.
- Frequent fluid intake
- Paracetamol for fever
- Cough linctuses to suppress dry cough
- Antibiotics to prevent secondary infection
- Prevention: active or passive immunization.

CHICKENPOX (VARICELLA)

- Organism: Varicella-zoster virus
- Age: Mostly children under 10 years. It is uncommon in adults in whom the disease tends to be more severe.
- Spread: by droplet infection.

CLINICAL FEATURES

Constitutional symptoms are usually brief & mild (headache, fever, sore throat).

Rash

Rash in crops at first on back, then chest, abdomen, face and lastly limbs.

Character: at first macule, in few hours dark pink papule which soon turns into vesicle and within 24 hours into pustule. The vesicles are elliptical or oval with axis parallel to the ribs.

Distribution: rash in more on upper arms and thighs, upper part of face and in flexures.

Scab formation: Pustules rupture & dry to form scab within 48 hours of appearance.

Pruritus, lymphadenopathy.

COMPLICATIONS

Direct viral effects

- Pneumonia (usually adults or immunosuppressed)
- Myocarditis (usually adults or immunosuppressed)

Post-viral effects

- Encephalitis (cerebellar)
- Glomerulonephritis

Secondary bacterial infection

- Skin
- Septicaemia
- Osteomyelitis/septic arthritis

Intra-uterine infection

- Congenital limb defects (rare)

MANAGEMENT

1. Bed rest
2. For pruritus; calamine lotion and antihistamine
3. Local antiseptic e.g. chlorhexidine should be applied to the skin if there is secondary infection.
4. Antibiotics – for secondary infection.
5. Antiviral drugs: acyclovir (Zovirax 200mg) 800 mg 5 times daily.

INFECTIOUS MONONUCLEOSIS

- Organism: Epstein – Barr virus
- Age: Old children & young adults
- Spread: Oral contact (exchange of saliva)

CLINICAL FEATURES

- Fever, sore throat, myalgia
- Exudative tonsillitis
- Petechial rash on palate
- Lymphadenopathy (especially posterior cervical chain)
- Splenomegaly (in 50%)

- Maculo-papular rash: It occurs in less than 15% of patients unless ampicillin has been given for sore throat in that cases rash occurs in more than 90% of patients.

INVESTIGATIONS

- Atypical lymphocytosis, granulocytopenia
- Positive Monospot test within 4 weeks after onset of illness.
- Elevation of liver enzymes

COMPLICATIONS

- Chronic fatigue syndrome (common)
- Hepatitis (rare)
- Hemolytic anemia (rare)
- Thrombocytopenia (rare)
- Rupture of spleen (rare)
- Meningo-encephalitis (rare)
- Guillain – Barre syndrome
- Interstitial nephritis
- Pseudocroup (cough, dyspnea)
- Myocarditis

D/D:

- Cytomegalovirus
- Toxoplasmosis
- Acute HIV infection (AIDS)

All these conditions present with lymphadenopathy, splenomegaly and fever with an atypical lymphocytosis (but sore throat is usually not present in these conditions.

MANAGEMENT

1. Rest
2. Symptomatic treatment.
3. Corticosteroids in case of impending airway obstruction from enlarged lymph nodes, hemolytic anemia, and severe thrombocytopenia.
4. Management of complications; rupture of spleen requires emergency splenectomy. Rupture of spleen occurs due to deep palpation or vigorous activity.

HERPES SIMPLEX INFECTION

Organism: Herpes simplex virus type 1 & type 2
Clinical features: infection may be primary or recurrent.
Primary infections: Ulcerative stomatitis (commonest in infants), keratitis, finger infections, vulvo-vaginitis, balanitis & encephalitis

Recurrent infections: these are commonest at the lips and adjoining skin (herpes labialis). Genital lesions also commonly recur.

Management
- Mild infection – no treatment
- Severe – Acyclovir oral, I/V & eye drops available.

ZOONOTIC DISEASE (animal to human)
Tapeworms, Toxoplasmosis, Trichinella, salmonella, Campylobacter, E.coli, tuberculosis, brucellosis, listeriosis, leptospirosis, toxocara, hydatid cyst, rabies, psittacosis.

MUMPS

Mumps is a paramyxoviral disease spread by respiratory droplets that usually produces inflammation of parotid glands.
- Most patients are children.
- Incubation period is 14-21 days.
- Infectivity occurs via saliva and urine.

CLINICAL FEATURES

Classical tender parotid enlargement, which is bilateral in 75%, follows a prodrome of low-grade fever and malaise. High-grade fever occurs if there is meningitis or orchitis develop as a complication of mumps.

Usually there is one gland swelling initially then after 1-3 days other gland enlarges and sometimes second gland enlarges after the recovery of first gland.

COMPLICATIONS

Orchitis
Orchitis develops typically 7-10 days after the onset of parotitis occurs in about 25-40% of postpubertal men. Bilateral orchitis is seen in 33% of patients involved. Sterility is rare.

Oophritis
Lower abdominal pain and ovarian enlargement suggest inflammation of ovaries.

Meningitis
Meningitis occurs in about 30% of cases presenting with fever, headache, neck stiffness, and lethargy.

Pancreatitis
Mumps is a leading cause of pancreatitis in children presenting with upper abdominal pain, nausea and vomiting.

Rare complications
- Transient hearing loss and larynthitis due to 8th nerve neuritis.
- Encephalitis
- Guillain – Barre syndrome
- Thyroiditis
- Hepatitis
- Neuritis
- Myocarditis
- Thrombocytopenia
- Nephritis

INVESTIGATIONS
- **CP:** relative lymphocytosis.
- **Serum amylase** is commonly elevated with or without pancreatitis because of salivary gland involvement.
- **CSF:** lymphocytic pleocytosis and normal to low glucose in meningitis.
- **Diagnosis** of mumps is confirmed by isolating the virus from saliva or CSF or demonstrating 4- fold rise in complement fixing antibodies.

MANAGEMENT
Patient should be isolated until swelling subsides and kept at bed rest during the febrile period. Treatment is symptomatic.

Management of complications

Orchitis
- Scrotum should be suspended with scrotal support and ice bags applied.
- Incision of tunica may be required in severe cases.
- Analgesics for pain. Pain may also be relieved by injection of spermatic cord at the external inguinal ring with 1% procaine solution.
- Hydrocortisone (Inj. Solu- cortef) 100 mg IV followed by prednisolone 20 mg orally 6-hourly for 2-3 days.

Meningitis
Symptomatic
Treatment of cerebral edema with mannitol or steroids.

Pancreatitis
Symptomatic treatment.

HIV --- AIDS

Human immunodeficiency virus (HIV) is the cause of acquired immune deficiency syndrome (AIDS). HIV destroys CD4 lymphocytes resulting in impairment of cell - mediated immunity with consequent susceptibility to opportunistic infections.

MODES OF TRANSMISSION

HIV is present in blood, semen and other body fluids such as breast milk and saliva. Exposure to infected fluid leads to a risk of acquiring infection, which is dependent on the integrity of the exposed site, type and volume of body fluid, and viral load.

Major modes of transmission are:

1. **Sexual:** transmission risk after exposure to genital mucus membrane is 0.2-0.5% and less than 0.1% for non- genital mucus membrane.
2. **Parenteral:** transmission in recipients of blood or blood product and injection drug users.
3. **Vertical:** from mother to baby.

RISK FACTORS

Following are the important factors increasing the risk of acquisition of HIV infection:

Sexual transmission

- Sexually transmitted infections, especially genital ulcers.
- Menstruation
- Non- circumcised
- Increased number of sexual partners.
- Rectal or vaginal trauma

Injection drug use transmission

- Sharing needles
- Frequency of use
- Prostitutes
- Intravenous use

Occupational transmission (nurses, doctors, lab. workers)

- Deep injury
- Visible blood on device

Vertical transmission (peripartum and breast feeding)

- Older gestational age
- Lower birth weight
- Prolonged rupture of membranes
- Fetal trauma
- No paripartum prophylaxis.
- Vaginal delivery.
- Longer duration of breast feeding
- Mastitis

NATURAL HISTORY

Primary infection / seroconversion

Primary infection is symptomatic in 70-80% o cases and usually occurs 2-4 weeks after exposur (incubation period).

The major clinical features are:

- Fever
- Erythematous maculopapular rash mainly over trunk.
- Fatigue
- Pharyngitis with cervical lymphadenitis. Headache, arthralgia and myalgia.
- Mucosal ulceration (mouth, genital).
- Neurological presentation (rare) manifesting as aseptic meningitis, encephalitis, myelitis, polyneuritis.
- Opportunistic infections such as oropharyngeal candidiasis, pneumocystis carinii pneumonia (rare).

Symptomatic recovery occurs in 1-2 weeks but may take up to 10 weeks.

Asymptomatic infection (clinical latency)

Asymptomatic infection follows for a variable period during which the infected individual remains well with no evidence of disease except for possible presence of persistent generalize lymphadenopathy. The virus continues to replicat and the person is infectious. The median time is 1(years from infection to development of AIDS. Older age is associated with more rapid progression.

Mildly symptomatic disease

These patients present with chronic weight loss, fever, diarrhea, oral or vaginal candidiasis, oral

hairy leukoplakia, recurrent herpes zoster, severe pelvic inflammatory disease, cervical dysplasia and ITP.

Acquired immunodeficiency syndrome (AIDS)

Acquired immunodeficiency syndrome is defined by the development of specified opportunistic infections and tumors. As H!V infection progresses the viral load rises, CD4 count falls and clinical features as a result of immunosuppression.

CLINICAL SYNDROMES IN HIV

Mucocutaneous manifestations
- Pruritus, dry itchy skin, pruritic popular eruption.
- Drug reactions are common
- Aphthous ulcers

Gastrointestinal effects
Weight loss, diarrhea, wasting and anorexia.
Cryptosporiodiosis (acute diarrhea)

Eye disease
CMV retinitis, acute uveitis.

Hematological complications
Anemia, neutropenia, thrombocytopenia

Renal complications
Nephrotic syndrome due to HIV- associated nephropathy.

Respiratory complications
- Pneumocyctic carinii pneumonia
- Histoplasmosis (pneumonia)
- Aspergillus infection
- Tuberculosis

Cardiac complications
Cardiomyopathy causing cardiac failure.

Neurological diseases
- AIDS dementia complex
- Sensory polyneuropathy causing paraesthesias
- Aseptic meningitis
- Toxoplasmosis (encephalitis and cerebral abscess)

HIV – RELATED SKIN DISEASES

Early HIV

Infections
- Herpes simplex
- Varicella zoster
- Impetigo
- Dermatophyrosis
- Scabies
- Syphilis

Other
- Psoriasis
- Xeroderma

Late HIV
- Kaposi's sarcoma
- Molluscum contagiosum
- Non- Hodgkin's lymphoma
- Cryptococcus
- Histoplasmosis

HIV –RELATED GASTROINTESTINAL DISEASES	
Esophagus	Candida, herpes simplex, CMV, Kaposi's sarcoma, aphthous ulcers
Small bowel	Cryptosporidium, microsporidium, CMV.
Large bowel	Salmonella, CMV, Cryptosporidium, clostridium difficile
Biliary tract	Cryptosporidium, CMV
Liver	Hepatitis B, C, CMV, tuberculosis

HIV –RELATED RESPIRATORY DISEASES	
Diffuse infiltrates	Pneumocystis carinii pneumonia, non- Hodgkin lymphoma, atypical bacterial pneumonia.
Nodules	Kaposi's sarcoma, cryptococcus, bacterial pneumonia,tuberculosis
Hilar lymphadenopathy	Tuberculosis, Kaposi's sarcoma, lymphoma, cryptococcus, histoplasma
Pleural effusion	Kaposi's sarcoma, tuberculosis, bacterial pneumonia, cavity based lymphoma

HIV -RELATED CNS DISEASES	
Brain	Toxoplasma, primary CNS lymphoma, progressive multifocal leucoencephalopathy
Meningitis	Cryptococcus, tuberculosis, HIV, syphilis
Spinal cord	HIV, transverse myelitis
Peripheral nerves	HIV, non- Hodgkin's lymphoma.

INVESTIGATIONS

HIV antibody: Confirmation of HIV is by ELISA antibody testing.
PCR for HIV RNA.
Viral load (HIV RNA): by PCR or bDNA or NASBA method.
Absolute CD4 count.

MANAGEMENT

Antiretroviral drugs

Nucleoside reverse transcriptase inhibitors

- Zidovudine (AZT)
- Didanosine
- Lamivudine

Non- nucleoside reverse transcriptase inhibitors

- Efavirenz
- Nevirapine

Protease inhibitors

- Saquinavir
- Indinavir

VIRAL HEMORRHAGIC FEVER

The viral hemorrhagic fever syndrome is a group of findings due to increased permeability and disruption of microvasculature causing local hemorrhage, decreased blood pressure that may lead to shock. Dangue virus is the common cause of viral hemorrhagic fever epidemic in Karachi, while other viruses are yellow fever virus, Congo virus and Hanta virus.

DANGUE FEVER

Dangue virus is transmitted by the bite of aedes mosquito.

Clinical features

- There is sudden onset of fever with chills and severe aching (breakbone) of head back and extremities.
- Sore throat, prostration, headache, dizziness, photophobia, abdominal or chest pain, nausea, vomiting, insomnia and depression are also accompanied.
- The initial febrile phase lasts 3-7 days followed by remission of a few hours to days.

On examination

- There may be conjunctival redness and flushing or blotching of the skin.
- Rash appears in 80% of cases during the second febrile phase. Rash appears first on the dorsum of the hands and feet and then spreads toarms, legs, trunk and neck. Face is rarely involved.
- Bleeding tendency: tourniquet test (when tourniquet is used to withdraw blood or cuff is applied for BP measurement, it leaves reddish mark due to damage of vessels.
- Petechial rashes and GI bleeding may occur.
- Tenderness to palpation of muscles, periorbital edema, hypotension and tachycardia may be present on examination.

Investigations

- Blood CP: leukopenia, thrombocytopenia.
- Virus detection from blood.

Complications

- Bleeding from nose, gums, hematuria or GI bleeding.
- Bone marrow failure
- Depression
- Pneumonia
- Iritis
- Orchitis
- Dangue shock syndrome: hypotension, hepatomegaly, pleural effusion, cyanosis, ascites, echymosis and GI bleeding.

Prevention

- Control of mosquitoes by insect repellents.
- Patient's isolation and strict barrier nursing are not required.

Differential diagnosis

- Malaria
- Typhoid
- Leptospirosis
- Shigellosis
- Rickettsial disease

Treatment

- Intravenous saline for hypotension.
- Paracetamol for pain and fever.
- Parenteral antiemetics
- Platelet monitoring is essential, platelet replacement may be required.

DIAGNOSIS OF INFECTION

HISTORY

CLINICAL EXAMINATION:

Particular attention to skin rashes, lymphadenopathy and hepatosplenomegaly

INVESTIGATIONS

1. **Blood CP**
    - Polymorphonuclear leucocytosis – in bacterial infection.
    - Neutropenia: viral infections, brucellosis, typhoid
    - Lymphocytosis: viral infections, whooping cough
    - Atypical lymphocytes: Infectious mononucleosis
    - Eosinophilia: Parasitic infections, helminthes
2. Urine D/Reactants,
3. X-ray chest
4. Blood clture
5. Microscopic examination & culture of body fluids e.g. urine, faces, CSF, Sputum
6. Tissue biopsy/aspiration
7. Ultrasound & CT Scan

ANTIMICROBIAL CHEMOTHERAPY

Choice of drug

- Depends on culture & sensitivity
- Blind therapy (before c/s report) depends on knowledge of the organisms likely to be involved. Before beginning blind therapy it is necessary to obtain appropriate body fluids or other specimens for microbiological examination. Adjustment to the antibiotic regimen can then be made, if necessary, when antibiotic sensitivity is available.

Spectrum of activity

- Narrow spectrum antibacterial – when organism is known (e.g. penicillin & aminoglycosides)
- Broad spectrum – when blind therapy (e.g. cephalosporin, chloramphenicol & tetracycline).

Bactericidal vs. bacteriostatic

Bactericidal drugs: Penicillin, cephalosporin, aminoglycosides are more effective than bacteriostalic e.g. chloramphenicol, slfonamides & tetracyclines.

Renal & hepatic functions

Impaired renal or hepatic function necessaitates a major modification of the dose regimen or even complete avoidance of certain drugs.

Route of administration

If patient can take orally, there is no advantage of parenteral therapy.

Combination antibiotic therapy

Combination therapy is used in empirical treatment of many serious infections such as septicaemia, meningitis, tuberculosis and endocarditis.

ANTIMICROBIALS

PENICILLINS

Natural Penicillins

- Penicillin G IV.
- Benzathine penicillin IM.
- Procaine penicillin IM.
- Penicillin V (oral).

Spectrum of activity

Natral penicillins are more active against gram positive organisms, less active against gram negative and susceptible to hydrolysis by beta-lactamases. They are used in the following infections.

1. Beta-hemolytic streptococci.
2. Penicillin susceptible strep, pneumoniae.
3. Non-beta- lactamase producing staphylococci.
4. Gonococci, meningococci.
5. Treponema pallidum (syphilis).
6. Anaerobes e.g. clostridia (but not bacteroides).

Clinical uses

1. Meningitis, endocarditis.
2. Beta-hemolytic streptococcal pharyngitis.
3. Syphilis
4. Prophylactic for endocarditis, tetanus and gas gangrene.
5. Mild respiratory skin and soft tissue infection.

Aminopenicillins

a) Ampicillin (Penbritin).
b) Amoxicillin (Amoxil)

Spectrum of activity

1. Antibacterial spectrum of natural proteins plus
   - E. coli, proteus.
   - Salmonella, shigella
   - Beta-lactamase negative H. influenza.
2. Amoxicillin is better than ampicillin due to its increased gastrointestinal absorption, decreased incidence of diarrhea and less frequent dosing.

Clinical uses

Bronchitis, sinusitis, otitis, urinary tract infections, meningitis, typhoid, shigella dysentery.

Adverse effects

Same as that of natural penicillin.

Penicillinase – Resistant penicillins

- Methicillin IV.
- Oxacillin IV.
- Nafcillin IV.
- Dicloxacillin (oral).
- Cloxacillin (Ampiclox IV, IM, Oral).

Clinical uses

1) They are relatively resistant to destruction by beta-hemolytic staphylococci, therefore used in staphylococcal infections.
2) Oxacillin, dicloxacillin and cloxacillin are used in minor infections while nafcillin in serious systemic infections.

Adverse effects

Same as of natural penicillin.

Penicillins combined with beta-lactamase inhibitors

The addition of beta-lactamase inhibitors (clavulanic acid, sulbactam, tazobactum) can prevent inactivation of the parent penicillin by beta-lactamases produced by staph, aureus H-influenza, E.coli, and klebsiella.

- *Augmentin:* Amoxicillin + Clavulanic acid.
- *Unasyn*: Ampicillin + Sulbactam.
- *Zosyn:* Piperacillin+Tazobactam.

Spectrum of activity

Beta-lactamase producing staphylococcus aureus, H. influenza, N. gonorrhea, anaerobes.

Clinical uses

Beta-lactamase producing staphylococcus aureus, H.influenza, N. gonorrhea, anaerobes.

1. Augmentin is used for sinusitis and otitis media.
2. Other drugs may be used alone or in combination with aminoglycosides to treat the following infections:
   - Peritonitis due to ruptured viscus.
   - Osteomylitis in a diabetic patient.
   - Traumatic osteomyelitis.

Adverse effects.
Same as that of natural penicillins.

Ureidopenicillins

- Piperacillin
- Mezlocillin
- Azlocillin

Spectrum of activity
Gram negative bacilli especially pseudomonas infection.

Clinical uses
1. They are used in combination with aminoglycoside for serious pseudomans infections.
2. As an empirical therapy for fever in neutropenic patient.

Carboxypenicillins

- Carbenicillin
- Ticarcillin.

Spectrum of activity
Gramnegative bacilli.

Clinical uses
They are used in combination of aminoglycosides for the treatment of pseudomonal infection (e.g. UTI).

PENICILLINS AND CLINICAL USES

PENICILLINS	INDICATIONS
1. Benzyl penicillin.	– Infective endocarditis. – Pneumococcal, meningococcal and streptococcal infection. – Syphilis, tetanus, gas gangrene. – Actinomycosis, anthrax.
2. Benzathine penicillin.	– For rheumatic fever prophylaxis.
3. Ampicillin, amoxycillin.	– UTI. – Upper respiratory tract infection (sinusitis, bronchitis, otitis). – Typhoid fever.
4. Ampiclox, oxacillin, cloxacillin, Nafcillin, methacillin.	– Staphylococcal infection.
5. Augmentin.	– Upper respiratory tract infection (Sinusitis, otitis).
6. Unasyn, Zosyn, Timentin.	– Peritonitis, osteomyelitis.
7. Piperacillin.	– Gram negative bacilli infection e.g UTI, sepsis.
8. Carbenicillin, Ticarcillin.	– Gram negative infection e.g UTI.

CEPHALOSPORIN

First generation

- Cephalexin (Ceporex) oral, injectable.
- Cephradine (Velosef) oral, injectable.
- Cefazolin (Cefamezin) injectable.

Second generation

- Cefuroxime (Zinnat) oral, injectable.
- Cefactor (Ceclor) oral,
- Cefamendol (Mandol) injectable.

Third generation

- Cefotaxime (Claforan) injectable.
- Ceftazidime (Forturm) injectable.
- Ceftizoxime (Cetizox) injectable.
- Ceftriaxone (Rocephin) injectable.
- Cefixime (Cefspan) oral.

* Gram positive coverage decreases while the gram negative coverage increases from first generation to third generation.

First generation cephalosporin

Spectrum of activity

- Very active against gram positive cocci (strept, staph, pneumococci).
- Less active against gram negative bacilli (only active against E.coli and klebsiella).

Clinical uses

- Surgical prophylaxis.
- Urinar tract infection.
- Minor staphylococcal infection.
- Cellulitis, soft tissue abscess.

Adverse effects

- Nausea, vomiting, diarrhea (most common).
- Rash.
- Pseudomembranous colitis.

Second generation cephalosporins

Spectrum of activity

Organism covered by first generation + extended gram-negative coverage (active against proteus,enterobacter. H. influenzae).

Clinical uses

- Cefuroxime and cefactor are used for sinusitis otitis media and community acquired pneumonia.
- Cefuroxime can be used for meningitis.

Third generation cephalosporin

Spectrum of activity

- Active against staphylococcus (but less active than first generation) and streptococci.
- More active against gram engative bacteria than first and second generation.

Clinical uses

- Meningitis
- Ceflazidime (Fortum) is the most active cephalosporin against pseudomonas. It is also used empirically in the febrile neutropenic patient.
- Cefriaxone (Rocephin) is also indicated for gonorrhea.
- Sepsis of unknown cause in the immunocompetent patient.
- Fever in immunocompromised neutropenic patient (in combination with an aminogly coside).
- Cefixime (Cefspan) can be given in children for sinusitis and otitis media.
- Gram negative infection.

MACROLIDES

Erythromycin

Clinical uses

- Drug of first choice for legionella, mycoplasma corynebacteria and chlamydia.
- Also effective in streptococcal and pneumococcal infection.

Adverse effects

- Nausea, vomiting, diarrhea.
- Cholestatic hepatitis.
- Reversible hearing loss at high doses.

AZALIDES

It is a group of antibiotics closely related to the erythromycin.

- Azithromycin
- Clarithromycin (klaricid).

Spectrum of activity

Organism sensitive to erythromycin PLUS:

- more effective against H. Influenzae and pneumococci than erythromycin.
- Also effective for M. avium intracellulare.

Clinical uses

- Streptococcal pharyngitis.
- Mild to moderate upper and lower respiratory infections.
- Skin and soft tissue infections.
- Used in combination with tetracycline and bismuth for Helicobacter pylori infection.
- Gastro intestinal side – effects are less common than erythromycin.

AMINOGLYCOSIDES

- Gentamicin
- Amikacin.
- Tobramycin
- Streptomycin
- Kanamycin
- Neomycin.

Spectrm of activity

- Gram negative bacilli.
- Streptomycin is also effective against M. tuberculosis. Brucella and Yersinia.
- Although some activity against gram positive bacteria but unreliable.

Clinical uses

- Sensitive gram negative infection (e.g. UTI).
- In low doses they are used in combination of beta-lactum drugs (peniccillins and cephalosporins) for synergistic effect.
- Neomycin – Tropical infections of eye & skin. Bowel sterilization before surgery & in hepatic encephalopathy.
- Genetamicin & tobramycin – Gram negative organism including pseudomonas.
- Beta-lactamase producing staphyloccal infection.
- Streptococcal faccalis.
- Amikacin & netilmicin – In gentamicin resistant cases. Spectrum same as of gentamicin.

Adverse effects.

Nephrotoxicity:

Neomycin is the most nephrotoxic and streptomycin is the least nephrotexic. Gentamycin tobramycin and amikacin have intermediate nephrotoxicity.

Risk factors for nephrotoxicity are:

- o Old age.
- o Hypotension
- o Concomitant use of other nephrotoxic drugs
- o Liver disease.

* Aminoglycoside nephrotoxicity is almost always reversible with drug discontinuation.

Ototoxicity

- Streptomycin, gentamycin and tobromycin are preferentially toxic to vestibular system.
- Amikicin and neomycin are toxic the auditory nerve.
- Risk factors for ototoxicity are:
  Advanced age.
  Concomitant use of frusemide (lasix) or ethacrynic acid..
- Ototoxicity is irreversible.

QUINOLONES

- Ciprofloxacin (Ciproxin).
- Ofloxacin (Tarivid).
- Levofloxacin (Cravit)
- Gatifloxacin (Quintec)
- Norfloxacin (Noroxin).
- Enoxacin (Enoxabid).
- Pefloxacin

Spectrum of activity

1. Active against gram negative organism including salmonella, shigella, campylobacter and pseudomonas.
2. Gram positive organism e.g. staphylococci are also sensitive but activity is only moderate.
3. levofloxacin anf gatifloxacin are also effective against streptococcus pneumoniae, therefore very commonly prescribed for respiratory tract infections.

Clinical uses

- Urinary tract infections.
- GI infections, typhoid fever, septicemia.
- Sexually transmitted disease e.g. gonorrhea.

Adverse effects

- Nausea, vomiting, diarrhea (coomon) Headache, dizziness, Seizures, Insomnia, Rash (occasionally).
- Acute renal failure and anaphylaxis may also develop.
- Prolong QT may occur; therefore use cautiously in patients receiving antiarrhythmic drugs such as amiodarone.
- Tendonitis and tendon rupture may occur especially with pefloxacin.

Contraindications.

Children below 18 and pregnancy (because it can arrest the growth of the child).

METRONIDAZOLE

Clinical uses

- Anaerobic bacterial infection particularly due to Bacteroids.
- Amoebiasis, giardiasis.
- Trichomonas vaginalis.
- Brain abscess Iwith Penicillin).
- Helicobacter pylori infection (in combination with amoxicillin and omeperazole).

Adverse effects

Stomatitis, nausea and diarrhea.

VANCOMYCIN

Active against most gram-positive organism particularly staphylococci and streptococci.

Clinical uses

- Severe staphylococcal infection.
- Severe enterococcal infection (in combination with aminoglycoside).
- Surgical prophylaxis.
- Pseudomembranous colitis (antibiotic associated enterocolitis).

COTRIMOXAZOLE (SEPTRAN)

Clinical uses

- UTI.
- Upper respiratory tract infection.
- Bacillary dysentery.
- Genital tract infection.
- Typhoid.
- Burn, wounds, boil.
- Eye & ear infections.

TETRACYCLINES

Use of Tetracycline is now limited

- Tetracycline, doxycycline – Used
- Acne.
- Rickettsia
- Mycoplasma
- Chlamydia
- Brucella.
- Coxiella Burnetii
- Coxiella Burnetii.

CHLORAMPHENICOL

- Enteric fever
- Meningitis (due to H. influenza).
- Topically used for purulent conjunctivitis.

Organism	Disease	Clinical features	Investigations	Management
Herpes simplex virus	1. Mucocutaneous disease	1. Herpes labialis, painful genital ulcers.	1. viral culture, PCR in serum	1. Oral ulcers: Topical acyclovir, Tab. Acyclovir 200mg 5 – times daily Genital ulcers: Acyclovir 400mg twice daily
	2. Ocular disease	2. Keratitis, blepharitis	2. Branching (dendritic) ulcer that stains with fluorescein.	2. acyclovir eye drops
	3. Encephalitis	3. Headache, fever, behavioral changes, seizures, coma.	3. EEG (involvement of temporal lobe), CSF white cells and PCR	3. Inj. Acyclovir 10mg/kg/ 8 hourly for 10 days
	4. Bell's palsy	4. Fascial palsy	4. NCV	4. No effect of acyclovir on palsy
	5. Esophagitis	5. Usually in AIDs	5. Endoscopic biopsy and culture	5. Inj. Acyclovir 10mg/kg/ 8 hourly for 10 days
	6. Erythema multiforme	6. Steven – Johnson's		6. Acyclovir
Varicella- zoster virus	1. Varicella (chickenpox)	• Ulcers on pharynx, face, scalp, trunk, lesser involvement of extremities. • Fever • Chances of secondary bacterial infections • *Complications*: interstitial pneumonia, ischemic stroke, hepatitis, Rye's syndrome	Direct immunofluorescent antibody staining of scraping from lesion	Acyclovir started during first 72-hours reduces the severity and shorten the duration of chickenpox and herpes zoster.
	2. Herpes zoster	• Maculopapular to vesicular eruption usually follows any root distribution mostly thoracic and lumber. • Ramsy – Hunt syndrome: facial palsy, lesions of external ear, tinnitus, vertigo and deafness due to geniculate ganglion involvement.	Same as above	Same as above

Organism	Disease	Clinical features	Investigations	Management
Epstein –Barr virus	Infectious mononucleosis	• Age: 10-35 yrs • Fever, sore thrat, myalgia • Lymphadenopathy, splenomegaly, rash, exudative pharyngitis • ***Complications:*** splenic rupture, myocarditis, Guillain – Barre, hepatitis, renal failure, airway obstruction due to pressure of lymph nodes on airways.	Atypical lymphocytes Lymphocytosis Granulocytopenia Thrombocytopenia Hemolytic anemia Heterophilic antibody test, Monospot test, LFTs usually deranged.	D/D CMV, toxoplasmosis, HIV, diphtheria. • Paracetamol, throat gargle • Corticosteroid if thrombocytopenia, hemolytic anemia, airway obstruction
CMV	• Mononucleosis – like disease in immunocompetent • Encephalitis, retinitis, esophagitis, pneumonia in immunocompressed	No sore throat	No heterophilic antibody	
Paramyxovirus	Mumps	Parotid swelling (other causes are cirrhosis, bulemia, sarcoidosis, parotitis, Sjogren synd, diabetes, other viruses, phenothiazines) Complications: orchitis, meningitis, pancreatitis, oophoritis, thyroiditis, hepatitis, myocarditis, nephritis, thrombocytopenia	Lymphocytosis Raied serum amylase	Bed rest, mouth wash, symptomatic Orchitis: NSAIDs, suspension, hydrocortisone, procaine injection in spermatic cord at external inguinal ring

Togavirus	Dengue hemorrhagic fever	• Transmitted by Aedes mosquito • High fever, chills, severe bodyache (break bone), sore throat • Conjunctival redness • Petechial rash sparing face – later desquamation • GI hemorrhage	Leukopenia, thrombocytopenia. viral antibodies.	Paracetamol and other symptomatic
Arbovirus	Yellow fever	• Transmitted by Aedes mosquito • Fever, retro- orbital pain, severe headache, bradycardia, jaundice, hemorrhage, hypotension, coma.	Leukopenia , proteinuria, PT prolonged. Igm capture enzyme immunoassay (EIA)	Symptomatic
coxsackievirus		Aseptic meningitis, myocarditis, hand – foot- and mouth disease, hepatitis, IDDM, glomerulopathy, throat ulcers		Symptomatic
Rhabdovirus	Rabies	• Sources: dogs, bats, cats • Transmitted by infected saliva causing encephalitis. • Incubation period: 3-7 days Pain at site of bite, paraesthesia, skin sensitive to air current, hydrophobia due to laryngeal spasm, excitibility, convulsions		• Cleansing the wound with soap, wound should not be sutured. • Postexposure prophylaxis: Immune globin 40units/kg – if not available then rabies antiserum 40 units/kg. • Human diploid cell rabies vaccine on 0. 3, 7, 14, 28 Treatment: no treatment, death after 7 days.
	Kawasaki syndrome	Fever, conjunctivitis, cracked lips, strawberry tongue, rash, cervical lymphadenopathy. Arteritis of coronary arteries may lead to myocardial infarction	Leukocytosis, elevated C- reactive protein MRA (angiography)	Aspirin 100mg/kg/d, corticosteroid Immune globin Plasmapharesis,
Coxiella burnetii (Rickettsiae	Q fever	• Transmitted by inhalation of dry feces, ingestion of infected milk of cattle, sheep, goats. • Fever, headache, cough, abdominal pain (mild	Antibodies	Tetracycline

Organism	Disease	Clinical features	Investigations	Management
Clostridium tetani	Tetanus Tetanospasmin released by bacteria interferes neurotransmission at spinal synapses of inhibitory neurons causing uncontrolled spasm	• Wound contaminated with soil and iv drug abuser are on risk. • Lock jaw, neck stiffness, dysphagia, hyperreflexia, spasm of abdomen, neck and back. • Spasm of glottis and resp. muscles leads to asphyxia.	D/D meningitis, phenothiazine toxicity	• Tetanus immune globin 5000 units I/M • Bed rest, sedation, mechanical ventilation • Penicillin 20milion units daily
Clostridium botulism	Botulism Botulism toxin inhibits release of acetylcholine at the neuromuscular junction	• Incubation period 12-36 hours • Diplopia, loss of accommodation, ptosis, cranial nerve palsy, impaired extraocular movement and fixed dilated pupil. • Dysphagia, dysphonia, nausea and vomiting. • Pt. Conscious, no fever. • Resp paralysis may lead to death	Toxin detection in serum and food	• Botulism antitoxin • Mechanical ventilation
Corynebacterium diphtheria	Diphtheria	Nasal, pharyngeal, laryngeal and cutaneous forms. Gray membrane covers pharynx in pharyngeal diphtheria. Complications: due to exotoxin • Myocarditis: heart block, arrhythmia failure • Neuropathy: diplopia, slurred speech, difficulty in swallowing.	Culture	• Diphtheria antitoxin 40,000 units • Erythromycin 500mg4 – times daily for 14 days.
Brucella	Brucellosis Transmitted from ingestion of infected meat of cattle, unpasteurized infected milk	Insidious onset of weakness, wt loss, low grade intermittent fever, headache, back pain, abdominal pain, epididymitis. Lymphadenopathy, splenomegaly. Hepatomegaly (less common) **D/D** lymphoma, tuberculosis, HIV, malaria, fungal infection, typhoid, infectious mononucleosis **Complications** Spondylitis, arthritis, endocarditis, meningitis, pneumonitis, hepatitis, cholecystitis	Rising antibody titer	Doxycycline plus rifampicin for 21 days

Organism	Disease	Clinical features	Investigations	Management
Yersinia pestis	Plague Transmitted by contact with infected animals such as rodents, also by flea bite	• High grade fever, intense headache, myalgia, pneumonia • Axillary, inguinal or cervical lymphadenopathy that may suppurate and drain • Purpuric spots (black plague)	Gram stain of aspirate from lymph nodes may show organism. Antibody titer	Streptomycin 1g IM then 500mg 6-8 hourly plus tetracycline 2g.
Neisseriae gonorrhea	Gonorrhea Sexually transmitted	Urethritis with serous or milky discharge May involve prostate, epididymis, vagina, cervix <u>Disseminated disease</u> • Intermittent fever, arthalgia, skin lesions (maculopapular or hemorrhagic) few in number and peripherally located. • Arthritis, tenosynovitis, endocarditis, meningitis are complications.	• Gram stain of urethral discharge shows diplococci • Culture – gold standard • Ligase chain reaction (LCR) in cervical or urethral swab or urine gives rapid diagnosis.	• Single dose of ciproxin 500mg or ceftriaxone 125 mg • For comolications IV penicillin or ceftriaxone • Doxycycline 100mg for 5 days for coexisting chlamydia infection.
H. ducreyi	Chancoid Sexually transmitted	Vesiculopustule that becomes <u>painful ulcer</u> on genitalia with tender lymphadenopathy	Swab culture of lesion	Ciproxin 500mg 2times daily for 3 days
Clammactobactrium granulomatis	Granuloma inguinale Sexually transmitted	Painless ulcer on genitalia with beefy- red friable base of granulation tissue. Large ulcer may advance onto the lower abdomen and thighs.	Donovan bodies in tissue scrapping on Wright's stain	Tetracycline 500mg 4 – times daily for 21 days.
Chlamydia trachomatis	Lymphogranuloma venerum Sexually transmitted	• Ulcerative lesion on genitalia. • Massive enlargement of inguinal lymph nodes that break down to form multiple draining sinuses.	• Complement fixation test • Immunofluorescence test for IgM antibodies.	Tetracycline 500mg 4 – times daily for 21 days.

Organism	Disease	Clinical features	Investigations	Management
Mycobacterium leprae	Leprosy Transmission by inhalation	Involves skin, superficial nerves, eyes. <u>Lepromatous leprosy:</u> • Occurs in person with defective immunity. • Course is progressive and malignant. • Nodular skin lesions • Symmetrical nerve involvement e.g. bilateral ulnar neuropathy. • Abundant acid fast bacilli in skin lesion. • Negative lepromin skin test. <u>Tuberculoid leprosy:</u> • Cellular immunity is normal. • Course less progressive. • Macular anesthetic skin lesions. • Asymmetric nerve involvement. • Few bacilli in lesion. • Positive lepromin test.	Acid- fast bacilli in skin lesion.	Dapsone, clofazimine and rifampicin for at least 2-3 years.
Treponema pallidum	Syphilis Sexually transmitted	<u>Primary syphilis</u> • Painless ulcer (chancre) with indurated margins on genitalia or tongue or lip 2-6 weeks after exposure.] • Lesion is infectious. • Regional lymph node enlargement. <u>Secondary syphilis</u> • A few weeks to 6 months after development of chancre. • Skin: maculopapular generalized rash especially palms and soles. Condylomata lata on moist skin and mucus membrane. • Mucus membrane: ulcers on lips, mouth, throat, genitalia • Lesion is infectious. *Complications*: aseptic meningitis, cranial nerve paly, jaundice, nephrotic syndrome, alopecia and uveitis.	• Darkfield microscopy shows tremonema • VDRL • FTA - ABS	• Penicillin G 2.4 million units M once OR Doxycycline 100mg 2 times daily for 2 weeks. • As above

Organism	Disease	Clinical features	Investigations	Management
		<u>Tertiary syphilis</u> • Any time after secondary syphilis even after years of latency in 1/3 of untreated patients. • Infiltrative tumors (localized gumma) in skin, bones, liver. • Diffuse inflammation of CNS and large arteries causing neurosyphilis and aortitis. 1. Neurosyphilis : chronic meningitis, tabes dorsalis, general paresis (psychosis). 2. Aortitis: narrowing of coronary arteries causing ischemic heart disease, aortic regurgitation, aneurysm of ascending aorta. 3. Eye involvement may present with iritis, uveitis, optic neuritis.	CSF may show increased protein, lymphocytic pleocytosis, and a positive VDRL (however CSF may be normal in 30-70% cases).	Other than neurosyphilis: benzathine penicillin G 2.4 million units 3 times at 7 -day interval. Tetracycline in penicillin allergic patient. Neurosyphilis: Penicillin G 3 - 4 million units IV 4-hourly for 10-14 days
Leptospira	Leptospirosis Transmitted by ingestion of food or drink contaminated by the urine of rats, dogs or cats. Also transmitted from skin and conjunctiva – common in sewer workers.	<u>Anicteric form</u> Fever, chills, headache and myalgia of calf muscles. Marked conjunctival redness. <u>Icteric form</u> Renal and hepatic impairment with abnormal mental status. D/D acute viral hepatitis. Complications: renal failure, aseptic meningitis, myocarditis, pulmonary infiltrates.	• Leptospires can be detected from blood, CSF and tissues on darkfield examination during first 10 days then 4- fold rise in antibody titer. • PCR in blood, urine, CSF. • CPK elevated	Penicillin 6 million units IV daily or doxycycline 100mg twice daily.
Borrelia burgdorferi	Lyme disease Transmitted through tick bite	• Stage 1:flue – like symptoms and erythema migrans (red lesion on groin, thigh, or axilla). • Stage 2: weeks to months later - bell's palsy, aseptic meningitis, myopericarditis. • Stage 3: months to years later – arthritis of large joints.	Antibodies detection in serum	Doxycycline 100mg twice daily for 2-3 weeks. For CNS and cardiac involvement ceftriaxone 2g IV daily for 3-4 weeks.

Organism	Disease	Clinical features	Investigations	Management
Tryanosoma cruzi	Chagas disease Transmitted by reduvid bugs	<u>Acute</u> • Inflammatory lesion at the site of inoculation: • Eye: Romana's sign • Skin: chagoma • Hepatosplenomegaiy, lymphadenopathy <u>Chronic</u> Heart failure, megaesophagus and megacolon (due to damage to nerve plexus), constipation.	Antibodies	Nifurtimox
Leishmania donovani	Leishmaniasis (Kalazar) transmitted by bites of sand flies	• Nodule at the site of bite • Fever, sweats, weight loss, diarrhea. • Massive splenomegaly; hard nontender, hypersplenism • Hepatomegaly and generalized lymphadenopathy. • Hyperpigmentation of skin – hands, feet, abdomen, forehead	Antibodies Leukopenia, lymphocytosis, Marked increase in serum globulin LFTs deranged	Sodium stibogluconate
Toxoplasma gondi	Toxoplasmosis	<u>In immunocompetent patients</u> Infectious mnonucleosis like picture <u>In immunocompromised patient (Cancer, HIV)</u> • CNS: mass lesion with focal neurological deficit, seizures, headache, altered mental status. • Eye: retinitis • Lung: pneumonia	• Antibodies • Trophozoites • Characteristic tissue histology • Tissue culture • PCR	<u>Immunocompetent</u> • No treatment required <u>Immunocompromised</u> • Pyrimethamine
Schistosoma (Blood flukes) <u>Intestinal</u> S. mansoni S. Japonicum <u>Bladder</u> S. haematobium	Schistosomiasis Reservoir: man Intermediate host: snail Enter through skin or mucus membrane during swimming	<u>S. mansoni</u> • Acute: itchy papule at the site of penetration. • Chronic: Periportal fibrosis in liver (cirrhosis) – portal hypertension. <u>S. haematobium</u> • Dysuria, hematuria, bladder polyps, hemorrhagic cystitis, bladder cancer.	• Eggs in urine or stool • Antibodies through ELISA, immunoblot • Liver biopsy • cystoscopy	Praziquantel 20mg/kg twice in one day
Echinococcus granulosus	Hydatid cyst disease Definite host: dog Intermediate host: cattle, sheep Human infected when ingest food or water contaminated with eggs passed in dog	• Cyst may be present in liver (most common), lung, brain, bones, skeletal muscles, kidneys, spleen. • Liver cyst may remain silent for 10-20 years. • Liver cyst may present with right upper quadrant pain, nausea, vomiting. Biliary obstruction may lead to cholangitis, cirrhosis, portal hypertension. Cyst rupture causes anaphylaxis. • Pulmonary cyst may present with obstruction of bronchus and segmental collapse. • Brain cyst may present with seizures. • Cyst in vertebrae may cause compression of spinal cord and paraplegia	• Ultrasound, CT, MRI • Immunoblot test • Antibodies	• Albendazole • Surgical removal Scolicidal solutions e.g. 20% hypertonic saline, silver nitrate, ethanol. Albendazole and praziquantel preoperatively for 1 month

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POISONING 11

- Organophosphate poisoning
- Snake bite poisoning
- Benzodiazepine poisoning
- Lead poisoning
- Paracetamol (acetaminophen) poisoning
- Salicylate poisoning
- Opiates poisoning

ORGANOPHOSPHATE AND CARBAMATE INSECTICIDE SPOISONING

Organophosphate and carbamate insecticides are widely used in agriculture (for crop spray) and at home as insecticides for rodents, cockroach etc. Parathion, DDT, Finis, Baygon, Coopex are commonly used products. Most of the war gases are also organophosphates.

MODE OF ACTION

Organophosphates and carbamates are also called anticholinestrases because they inhibit the enzyme anticholinestrase resulting in an increased acetylcholine activity at nicotinic and muscarinic receptors and in the central nervous system.

Intoxication may follow:

- *Ingestion* (for suicide or accidentally).
- *Inhalation* (usually when spraying crops or even at home using insecticide spray for cockroaches and other insects).
- *Dermal absorption*

EFFECTS OF ACETYLCHOLINE
Through muscarinic receptors (antagonized by atropine)
• **CVS:** bradycardia, vasodilatation • **GIT:** increased tone, contraction, secretion and peristalsis of stomach and intestine. Relaxed sphincters. • **RESP:** increased bronchial secretions and bronchial constriction. • **EYE:** constriction of pupil (miosis) • **EXOCRINE GLANDS** : increased secretion of salivary, lacrimal, gastric, pancreatic, intestinal, nasopharyngeal and bronchial glands.
Through nicotinic receptors (not antagonized by atropine)
• Neuromuscular junction: causing muscle contraction. • Autonomic ganglia. • Adrenal medulla: secretion of adrenaline and noradrenaline. • CNS

Personal perspective and opinion

Ingestion of insecticide is very common for suicide attempts; most of the patients are young females using it as a tool to threat the family for their demands. Parents (or husbands) try to hide the situation and tell the story of accidental pesticide ingestion (they say "she ingested Finis considering as a cough syrup"). Actually parents are afraid of disrepute of their daughter and they avoid it to become a medico- legal case. Unfortunately majority of medico- legal officers at emergency demand bribe from the family to write it as an accidental case not the suicide attempt and the family is compelled to do so. Can anybody stop this malpractice?

CLINICAL FEATURES

Time from exposure to the onset of toxicity varies from minutes to hours but usually is between 30 min to 2 hours. Most patients recover within 24-48 hours but some insecticides may affect for weeks to months.

Muscarinic effects:

- ***GIT:*** nausea, vomiting, abdominal colic, diarrhea, tenesmus (due to increased gut motility) sweating, hypersalivation and fecal incontinence.
- ***RESP:*** dyspnea, cough, wheezing, increased bronchial secretions, pulmonary edema. Death is usually due to respiratory arrest.
- *Urinary:* increased urinary frequency and incontinence.
- EYE: Miosis, blurred vision.
- Heart: bradycardia, hypotension, heart block in severe cases.

Nicotinic effects

- Muscle twitching, fasciculations and muscle weakness. In severe cases paralysis of limb, respiratory and extraocular muscles.
- Hypertension and tachycardia.

CNS effects

Anxiety, restlessness, tremor, convulsions, confusion and coma.

COMPLICATIONS

1. **Loss of consciousness**
2. **Respiratory failure** (due to aspiration, excessive secretions, pneumonia, septicemia or ARDS). Cause of death is usually respiratory failure.
3. **Aspiration pneumonia:** due to vomiting in altered consciousness may be aspirated.
4. **Urinary tract infection.**
5. **Septicemia.**

DIAGNOSIS

Usually the diagnosis is clinical. History is available from the patient or relatives. It may be confirmed by measuring RBC and plasma cholinesterase activity: a reduction of cholinesterase activity in red blood cells and plasma to less than 50% of normal confirms the diagnosis of organophosphate poisoning.

MANAGEMENT

Oxygen: Admit the patient in ICU and give supplementary oxygen.

Gastric lavage: if the agent was recently ingested, empty the stomach by gastric lavage and administer activated charcoal.

- Do not induce vomiting because of risk of abrupt onset of seizures and aspiration.
- If the insecticide is on the victim's skin or hair, wash with soap and water.

Atropine: atropine reverses excessive muscarinic stimulation and is effective treatment of salivation, wheezing, abdominal. cramp and sweating.

Administer atropine 2 mg IV every 15 min until bronchial and other secretions are controlled. Repeated doses or constant atropine infusion (0.02-0.08 mg/kg/hour) may be necessary for several days. Atropine causes tachycardia, if heart rate is more than 130/min then for protection of heart reduce the heart rate with IV diltiazem or propranolol (we have IV verapamil instead of diltiazem and metoprolol instead of propranolol in Pakistan).

Pralidoxime (Contrathion): It is a specific *antidote* that reactivates cholinestrases and is indicated for nicotinic symptoms due to organophosphate poisoning.
Dose is 1-2 g IV over 5-20 min (one vial of Contrathion contains 200mg pralidoxime and costs Rs. 500) i-e. 5-10 vials of Contrathion are diluted in 100 ml of water for injection. The dose may be repeated every 4-6 hours or start continuous infusion at the rate of 10 mg/kg/hr. Continue pralidoxime as long as there is any evidence of acetylcholine excess.

(Signs of full atropinization: dry hot skin, dry secretions, pulse more than 70/min and dilated pupils).

Mechanical ventilation

Indications

- Excessive secretions
- Depressed level of consciousness: to protect the airway.
- Poor gas exchange unresponsive to supplementary oxygen .
- Severe metabolic acidosis with hemodynamic instability (systolic BP <90 mmHg).
- Cardiopulmonary arrest.

Mode of ventilator

SIMV + pressure support mode in either pressure controlled or volume controlled form. Positive end expiratory pressure is applied to keep oxygen saturation >94% at FIO2 40%.

Weaning from ventilator is usually carried out with pressure support weaning and T-tube trial.

SNAKEBITE POISONING

Snakebite is a common emergency in our hospitals, patients usually come from the rural areas, most of the time they are aware of the snake species. Students may get patient of snakebite as a long case in exams.

Common types of poisonous snakes

Poisonous species of snake fall into three families:

1. Viperideae: such as Russel viper, pit viper.
2. Elapidae: such as cobra, krait, coral snake.
3. Hydrophidae: such as sea snake.

PATHOGENESIS & CLINICAL FEATURES

Poisonous snakes have a pair of enlarged teeth called fangs in their upper jaws that inject venom into the tissues of their victim.

Snake venoms are complex mixtures of proteins and small polypeptides with enzyme activity.

Effects of venoms may be:

- Hematotoxicity: They cause the vasculature leaky resulting in local or systemic bleeding leading to hypotension and shock.
- Cytotoxicity: causing local tissue necrosis, mygolinuria and renal failure.
- Coagulopathy: causing bleeding or clotting disorders.
- Cardiotoxicity: causing myocardial depression and reduced cardiac output.
- Neurotoxicity: inhibiting peripheral nerve impulses leading to paralysis.

Viperidae :

- Local swelling, echymosis and blistering at the site of bite.
- Systemic involvement within 30 min including vomiting, hypotension and shock.
- Bleeding and clotting disturbances (coagulopathy): bleeding gums or venepuncture site, bleeding may be fatal.

Elapidae

- Usually no swelling at the site of bite.
- Vomiting, salivation.
- Hypotension and shock resulting from loss of intravascular fluid into the soft tissues.
- Neurological symptoms: muscle weakness causing ptosis, diplopia and dysphagia, with paralysis of respiratory muscles in severe cases.
- Myocardial depression causing reduced cardiac output and rhythm disturbances.

Hydrophidae (sea snake)

Muscle involvement causing rhabdomyolysis with myalgia and myoglobinuria that may lead to acute renal failure. Cardiac and respiratory paralysis may occur.

INVESTIGATIONS

1. Blood grouping and cross matching: as soon as possible before the effect of circulating venom interfere the blood grouping.
2. Complete blood count: to evaluate degree of hemorrhage and hemolysis.
3. Urea, creatinine and electrolytes: for renal status.
4. Liver function tests (LFTs).
5. PT, APTT, BT, CT, FDP : to assess coagulopathy.
6. Urine analysis: for hemoglobinuria and myoglobinuria.
7. ABGs may be required in severe cases.
8. ECG: to look for rhythm disturbances.
9. Chest X-ray

MANAGEMENT

- All patients with suspected snake bite should be observed for 12-24 hours, as initial manifestations may be delayed, especially with elapid bites.
- Reassuring the patient, not all snakes are poisonous and even bite by the poisonous snake may be "dry bite" i-e no venoum in the bite.
- Try to identify the type of snake.
- Immobilize the bitten area to minimize the venom spread.
- Application of firm bandage to occlude lymphatic drainage (not the arterial supply); use of tourniquet is discouraged because they do not prevent spread of venom.
- Incisions at the site of bite and attempts to suck out the venom with mouth should not be made.

- Pain and vomiting: symptomatic treatment. Aspirin should not be used for pain since this may aggravate bleeding.
- Saline and dopamine for hypotension.
- Monitor blood pressure, coagulation, renal, neurological and cardiorespiratory status.
- Large bore IV canulla should be inserted on un affected limb.

Antivenin:

- Antivenin is indicated in patient with severe or progressing local tissue local reaction at the site of bite, clinical or laboratory evidence of systemic involvement.
- In about 50% of snake bites no venom is injected (dry bite) and antivenoms are generally not indicated. However when indicated antivenom should be given early, as the antivenoms only neutralize venom they can not reverse the effects of venom. Allergic reaction is the frequent complication of antivenin.
- Antivenom should be given slow IV, the same dose being given to children and adults.
- Before starting antivenom a test dose is given; 0.02 ml of saline- diluted antivenom is injected subcutaneously and observed for at least 10 min for redness, hives, pruritus or other allergic reactions. A syringe containing 0.5 ml of 1:1000 adrenaline must be available to combat anaphylaxis whenever antivenin is administered. Adrenaline is given subcutaneously. However skin test does not always predict which patients will have allergic reaction to antivenom; a skin test may be false positive or false negative.
- Intravenous antihistamine and ranitidine should be given before starting antivenin infusion to limit the acute allergic reaction.
- In severe cases the antivenom infusion should be continued even with allergic reaction with closely controlled conditions and premedication with adrenaline, antihistamine and steroids.
- Antivenin should be diluted in 1000 ml of saline, Ringer's lactate or 5% dextrose water and should be given slowly, in children 20ml/kg.
- Physician should be at the bedside t[illegible] intervene in the event of an acute allerg[illegible] reaction. Total dose may be given in 1- hours. Further antivenin may be necessary i[illegible] clinical abnormalities worsen.
- Antivenom is usually available in big government hospitals. Administrators are requested to make sure the availability of this life –saving medicine.

BENZODIAZEPINES POISONING

- Benzodiazepines are used as tranquilizers and as sleeping pills.
- Poisoning is usually due to attempted suicide.
- Alprazolam (Xanax), lorazepam (Ativan), bromazipam (Lexotanil) are commonly used benzodiazepines.

CLINICAL FEATURES

Features develop within 30 min of an over-dose and include:

- Weakness, ataxia, dilated pupil, dysarthria, and drowsiness.
- Nystagmus and confusion are also observed. Minor hypotension may occur.
- Coma and respiratory depression can occur with short acting benzodiazepine such as midazolam (Dormicum) or if bezodiazepines are combined with other CNS depressants such as tricyclic antidepressants.

> You may also get a long case of benzodiazepine poisoning because it is also a very frequent emergency. Most of the patients are young females, usually they take one or two tablets and discard remaining tablets from the strip but show as they have taken the whole strip, however opposite may be the story. Therefore clinically assess the patient's condition; not completely rely on history.

MANAGEMENT

- Gastric lavage is not advised in pure benzodiazepine overdose.
- Activated charcoal should be given repeatedly to decontaminate GIT.

- Impaired consciousness requires particular attention to maintain airway. Pulse oximetry is needed to monitor oxygen saturation.
- Observation should be for at least 6 hours post- ingestion.

Flumazenil (Inj. Anexate 0.1mg) a competitive benzodiazepine receptor antagonist can reverse CNS and respiratory depression. It is given IV as incremental dose of 0.2, 0.3 and 0.5 mg at 1 min intervals until the desired effect is achieved or a total dose of 3-5 mg has been given.
Flumazenil is not given routinely in mild to moderate poisoning (required when there is CNS or respiratory depression). It is expensive, costs more than Rs. 3000/injection.
Flumazenil should not be given in patients who are chronic dependent on benzodiasepine or who have taken tricyclic antidepressants with benzodiazepines; in these patients seizure may be precipitated. Removal of drug through dialysis is not possible because 85 to 99% of drug is protein bound in the plasma.

LEAD POISONING (imp. exam question)

Lead is used in a variety of industrial and commercial products such as paints, cans, plumbing fixtures, leaded gasoline, improperly glazed ceramics, lead crystals, leafy vegetables grown in lead contaminated soil and storage batteries.
Lead produces adverse effects on CNS, GIT and blood.

METABOLISM
Lead is absorbed into the blood where 95-99% is sequestered in red cells, where it is bound to hemoglobin. Therefore lead is measured in whole blood rather than in serum. The largest proportion of absorbed lead is incorporated into skeleton; however it also appears in nails, hair, sweat, saliva and breast milk.

Toxicity occurs due to its affinity for cell membrane and <u>mitochondria</u>, therefore it interferes mitochondrial phosphorylation, Na+, K+ and calcium ATPase.

CLINICAL FEATURES

CHILDREN

Symptomatic
Symptomatic toxicity in children develops usually at blood level of 80µg/dl and is characterized by:

- Abdominal pain and irritability followed by lethargy, anorexia, pallor (due to anemia), ataxia and slurred speech.
- Convulsion, coma and death due to generalized cerebral edema and renal failure occur in severe cases.

Subclinical toxicity
Subclinical toxicity occurs at blood level >30µg/dl and causes learning disorders in children and motor neuropathy.
It presents with mental retardation, selective deficits in language, cognitive function, balance, behavior and school performance. Maximum impact occurs at around age 2 years.

ADULTS

Symptomatic
Symptomatic toxicity in adults develop when the blood lead level is > 80µg/dl for period of weeks and is characterized by:

- Abdominal pain, headache, irritability, joint pain, fatigue, anemia, peripheral motor neuropathy (e.g. foot drop, wrist drop), deficits in short-term memory and ability to concentrate.
- Lead –line appears on gingiva-tooth border after prolonged high level exposure.

Chronic subclinical

- Chronic subclinical intoxication causes:
- Interstitial nephritis, tubular damage, hyperuricemia (with increased risk of gout) and chronic renal failure.
- Hypertension.

<u>FOR BOTH CHILDREN AND ADULTS</u>

- Increased bone level is a risk factor for bone diseases, anemia and hypertension.
- Hyperthyroidism may cause lead toxicity by mobilizing stores of lead in bones.

INVESTIGATIONS

1. **Blood lead level:**
- Less than 10 μg/dl is considered non-toxic.
- Levels between 10-25 μg/dl is associated with impaired neurobehavioral development in children.
- Levels of 25-50 μg/dl may be associated with headache, irritability and subclinical toxicity.
- Levels of 50-70 μg/dl are associated with moderate toxicity.
- Levels >70-100 μg/dl are associated with severe poisoning.

2. **Blood CP:** microcytic anemia with basophilic stippling.
3. **Blood protoporphyrin:** elevated.
4. **Gamma aminolevillinic acid** (heme precursor) increases in plasma and urine.
5. **Nerve conduction velocity (NCV):** prolonged nerve conduction time due to peripheral demyelination usually of extensor muscles of hand and feet.
6. **X-ray bone:** increased density at metaphyseal plate and growing long bones (lead lines) can develop in children.
7. **UCE:** adults chronically exposed to lead can develop elevated serum creatinine.

MANAGEMENT

Emergency measure

Coma: maintain airway, other management of unconscious patient.

Convulsion: anticonvulsion therapy.

Activated charcoal and endoscopic removal for recent acute ingestion.

Chelating agents

EDTA, dimercaprol and penicillamine.

Indications for chelation: blood lead level > 55 μg/dl in children and 80 μg/dl in adults.

PARACETAMOL (ACETAMINOPHEN) POISONING

Paracetamol (called acetaminophen in USA) is a commonly used analgesic. After absorption it is metabolized mainly by glucuronidation and sulfation, with a small fraction metabolized via P450 to highly toxic reactive intermediate. This toxic intermediate is normally detoxified by cellular glutathion. With acute paracetamol overdose (>140 mg/kg or 7 g in an average adult) hepatocellular glutathion is depleted and reactive intermediate attacks hepatocytes and cause cell lysis.

- Paracetamol poisoning and its management is a very frequently asked question in exams.

CLINICAL FEATURES

Shortly after ingestion patient may have nausea, vomiting and pallor but there are usually no other signs of toxicity until 24-48 hours after ingestion. Within 24-48 hours hepatotoxicity appears by right upper quadrant tenderness and mild hepatomegaly. Renal function also may be impaired.

Laboratory evidence of hepatotoxicity appears including prolonged prothrombin time (PT), and elevation of bilirubin and aminotransferases (AST and ALT). Severe poisoning may cause hepatic failure. A 2- fold prolongation of PT and serum bilirubin > 4mg/dl on third to fifth day after ingestion indicate hepatotoxicity.

DIAGNOSIS

Serum paracetamol level above the lower line between 4-24 hours after ingestion indicates possible hepatotoxicity and need for antidote therapy.

MANAGEMENT

Activated charcoal causes GIT decontamination in patients who present within 4 hours of ingestion.

Acetylcysteine (antidote): in patients with a potentially toxic paracetamol level acetylcysteine is given. First give loading dose of 140 mg/kg orally followed by 70mg/kg every 4 hours, continue for 72 hours. Treatment with acetylcysteine is most effective if started within 8-10 hours after ingestion. Side effects of acetylcysteine are nausea, vomiting and epigastric discomfort.

SALICYLATE (ASPIRIN) POISONING

Salicylates uncouple cellular oxidative phosphorylation resulting in anaerobic metabolism and excessive production of lactic acid and heat.

A single dose of more than 200 mg/kg is likely to produce significant acute intoxication. Poisoning may also occur as result of chronic excessive dosing over several days. Half life of salicylates is 2-3 hours in small doses but it may increase to 20 hours or more in patients with intoxication.

CLINICAL FEATURES

1. **Mild intoxication**: Nausea, vomiting with gastritis.
2. **Moderate intoxication:** hyperpnea (deep and rapid breathing), tachycardia, tinnitus, and an elevated anion gap metabolic acidosis.
3. **Severe intoxication:** agitation, confusion, coma, seizures, cardiovascular collapse, pulmonary edema, hyperthermia and death. PT is prolonged.

DIAGNOSIS

Diagnosis is confirmed by measuring serum salicylate level. Patients with levels > 100mg/dl after an acute overdose are more likely to have severe poisoning. Patients with chronic intoxication may suffer severe symptoms with levels of only 60-70 mg/dl. ABGs show respiratory alkalosis with underlying metabolic acidosis.

MANAGEMENT

Gastric lavage followed by activated charcoal given every 2-4 hours.

Treat metabolic acidosis with IV sodium bicarbonate.

Alkalinization of urine enhances renal salicylate excretion by trapping the salicylate anion in the urine. Add 100 meq (two ampoules) of sodium bicarbonate to 1L of 5% dextrose in 0.2% saline and infuse this solution IV at a rate of 150-200 ml/h.

Hemodialysis may be life saving and is indicated for patients with severe metabolic acidosis, markedly altered mental status or significantly elevated salicylate levels (>100-120 mg/dl).

OPIOID POISONING

Morphine, heroin and other opioids decrease CNS activity and sympathetic outflow by acting on opiate receptors in the brain.

- Opioid poisoning may be your long case in viva exam.
- Heroin abuse is common in Pakistan because of protection given to the heroin - sellers by the police (who gets bribe from them). Moreover police is not interested in arresting heroin abusers because they are jobless and have no money to give for release.

CLINICAL FEATURES

Mild intoxication: euphoria, drowsiness and constricted pupils.

Moderate to severe intoxication: hypotension, bradycardia, hypothermia, coma and respiratory arrest. Pulmonary edema may occur. Death is usually due to apnea or pulmonary aspiration of gastric contents.

Propoxyphene may cause seizures and prolongation of QRS interval. Tramadol, dextromethorphan and meperidine also cause seizures.

Duration of effects of heroin is usually 3-5 hours, methadone intoxication may last for 48-72 hours.most opioids are detectable on urine toxicology screening.

MANAGEMENT

- Protect airway (to prevent aspiration).
- Assist ventilation (with oxygen and mechanical ventilation).
- Naloxone (Inj. Nalox 0.4 mg): it is a specific antidote that can rapidly reverse signs of narcotic intoxication. Give 0.4-2 mg IV and repeat as needed to awaken the patient to maintain airway protecting reflexes and spontaneous breathing. Duration of effect of naloxone is only 2-3 hours; therefore repeated doses may be required.

PSYCHIATRY 12

- Defense mechanisms of brain
- Personality disorders
- Anxiety disorders
- Panic disorder
- Phobic disorder
- Generalized anxiety disorder
- Obsessive compulsive disordèr
- Post-traumatic stress disorder
- Hysteria
- Conversion disorders
- Hypochondriasis
- Dissociative disorders
- Psychosis
- Illusions
- Schizophrenia
- Hallucination
- Delusional disorder
- Brief psychotic disorder
- Depression
- Bipolar disorders
- ECT
- Mania
- Delirium
- Dementia
- Substance abuse
- Anorexia nervosa
- Bulimia

PSYCHIATRY

Psychiatry is a Greek term meaning "mind healing" refers to the medical science that deals with the study, diagnosis, treatment and prevention of mental disorders. These disorders may result from disturbances in biological functions or from adverse influence of psychological or sociocultural factors. These mental disorders may involve either intellectual or emotional processes, verbal or non-verbal behavior.

DEFENSE MECHANISMS OF BRAIN

Human brain has some defense mechanisms that are individual's unconscious intrapsychic adjustments to the perception of internal or external reality to decrease anxiety and conflict. These mechanisms are unconscious psychic processes that attempt to alleviate anxiety and influence adaptation to stressful situations. In USMLE there are usually several questions from this section.

Denial

Denial is a failure to acknowledge a disturbing aspect of external reality. Patients deny the intolerable external reality.

For example, a patient dying of cancer may deny impending death and make plans for future. Similarly loss or death of a loved person may be denied, so that the individual believes and acts as though the lost loved one were still present or would soon return. The denial may be observed in a patient who becomes euphoric or even manic following a very significant loss, or in other circumstances that would normally result in grief.

Repression

In this defense mechanism there is involuntary relegation (removal) of unbearable ideas and impulses into the unconscious.

Repression must be distinguished from *suppression* which is not an unconscious defense but a conscious effort to control unacceptable impulses, thoughts, feelings or acts.

Reaction formation

This is a process in which attitude and behavior are adopted that are the opposites of the impulses to which the individual is reacting. An unacceptable thought or feeling is transformed into its opposite. For example the mother who unconsciously hates an unwanted child may react toward this child by overprotection and overindulgence. A person with strongly repressed sexual impulses may take an active part in campaign for censorship of movies, perhaps even assuming the role of one of the censors, so that he himself is exposed to the material from which others are to be "protected".

Overcompensation

This is a conscious or unconscious process in which a real or fancied physical or psychological deficit inspires exaggerated correction. For example congenital or acquired bodily defects sometimes lead to efforts to overcome them, and a few such handicapped individuals have become world-renowned athletes.

Rationalization

This mechanism consists of unconscious efforts to justify or make acceptable certain feelings, behaviors or motives that would otherwise be threatening, through belief in explanations that are actually invalid. For example, hostile, and punitive behavior of teacher toward students may be rationalized as concern for their welfare. Another example is "sour grapes" whereby failure becomes less painful.

Intellectualization

It involves excessive use of intellectual processes and logical arguments as a means of avoiding stressful emotional experiences.

Projection

In this defense mechanism unacceptable emotions, motivation, guilt and behavior are not only denied but also attributed to (projected onto) other individuals. In this way the individual transforms anger at himself into anger towards others.

Identification

Identification involves identifying oneself with another person who is perceived as admirable or more powerful. In this process an individual unconsciously models

behavior and attitudes after those of another person, viewing himself as similar to that person. For example, a hospitalized child decides that he wants to be a doctor and asks for stethoscope of his own.

Introjection
In this process, an individual absorbs aspects of another person into his own self-image.

Isolation
Isolation describes the separation of a thought from its attached emotional tone, thereby making it tolerable. This mechanism is commonly helpful to physicians, who must detach themselves from feeling about their patient's suffering in order to function effectively.

Displacement
This is process whereby a feeling is redirected from its original object or person onto a more acceptable or less dangerous substitute. For example, a patient who was badly injured in an accident becomes angry with his surgeon for leaving a small scar during reconstructive procedures. Another example, hostile feeling against parents due to some childhood experiences are displaced onto others of the same sex as the parent.

Undoing
It involves performing an activity that is the opposite (actually or symbolically) of an impulse being repressed. For example, a person recently diagnosed with a malignancy becomes excessively concerned with nutrition, exercise and healthy lifestyle.

Acting out
This term is applied to behaviors unconsciously motivated by repressed conflicts or impulses. Foe example, one interpretation of antisocial behavior is that it represents a defense against anxiety associated with unconscious conflicts.

Conversion
In this mechanism unconscious conflicts are given symbolic external expression in the form of various bodily symptoms, such as loss of sensation, paralysis that have no underlying organic pathology.

Regression
It is characterized by an individual's return to more immature levels of functioning.

Sublimation
It occurs when unacceptable impulses are diverted into more acceptable activities such as various forms of creative activity.

Substitution
Displacing the emotion to a more acceptable form of activity. For example murderous impulse is replaced with a minor aggression or release it in some impersonal destructive act such as chopping wood or striking a punching bag.

DEFENSE MECHANISMS OF BRAIN	
Denial	Denial is a failure to acknowledge a disturbing aspect of external reality.
Repression	Involuntary relegation (removal) of unbearable ideas and impulses into the unconscious.
Reaction formation	Attitude and behavior are adopted that are the opposites of the impulses to which the individual is reacting
Rationalization	Unconscious efforts to justify or make acceptable certain feelings, behaviors or motives that would otherwise be threatening, through belief in explanations that are actually invalid
Projection	Unacceptable emotions, motivation, guilt and behavior are not only denied but also attributed to (projected onto) other individuals.
Introjection	In this process, an individual absorbs aspects of another person into his own self-image.
Undoing	Performing an activity that is the opposite (actually or symbolically) of an impulse being repressed
Displacement	A feeling is redirected from its original object or person onto a more acceptable or less dangerous substitute
Substitution	Displacing the emotion to a more acceptable form of activity.
Sublimation	Unacceptable impulses are diverted into more acceptable activities such as various forms of creative activity.
Isolation	Separation of a thought from its attached emotional tone, thereby making it tolerable.
Regression	It is characterized by an individual's return to more immature levels of functioning
Conversion	Unconscious conflicts are given symbolic external expression in the form of various bodily symptoms
Acting out	To behaviors unconsciously motivated by repressed conflicts or impulses.

PERSONALITY DISORDERS

PERSONALITY

Personality is the person's patterns of behavior that affect interpersonal relationships and social skills. These patterns are assumed to evolve from a combination of innate and learned tendencies, and to be modified by life stresses and neurologic changes.

PERSONALITY DISORDERS

These are maladaptive patterns of behavior that are often recognizable by the time of adolescence and rend to persist throughout a person's lifetime. Personality disorders result in marked impairment in social and occupational function and often provoke retaliation by others.

TYPES OF PERSONALITY DISORDERS
Odd or eccentric
• Paranoid personality disorder • Schizoid personality disorder • Schizotypal personality disorder
Dramatic, emotional
• Antisocial personality disorder • Borderline personality disorder • Histerionic personality disorder • Narcissistic personality disorder
Anxious or fearful
• Avoidant personality disorder • Dependent personality disorder • Obsessive-compulsive personality disorder

PARANOID PERSONALITY DISORDER

Individual with this disorder tend to be mistrustful and suspicious of the motivations and actions of others. They are often secretive and isolated, and they tend to be emotionally cold and odd.

It is more common in males. Schizophrenia and delusional disorder are more common in relatives of individuals with paranoid personality disorder.

Management

- Psychotherapy in mild cases.
- Antipsychotics in severe cases.

SCHIZOID PERSONALITY DISORDER

Individuals with this disorder are usually emotionally distant and seemingly derive little joy from living. They appear uninterested in interacting with others and indifferent to praise or criticism.

It is more common in males. Schizophrenia is common in relatives of individuals with schizoid personality disorder.

Management

- Psychotherapy
- Antidepressant medication

SCHIZOTYPAL PERSONALITY DISORDER

Individual with schizotypal personality disorder are socially isolated and uncomfortable interacting with others. In contrast to schizoid personality disorder they have odd manners of speech and affect, disturbance in thinking and perception abnormalities such as recurrent illusions.

It is more common in males.

Management

- Psychotherapy
- Antipsychotic medications.

ANTISOCIAL PERSONALITY DISORDER

Individual with this disorder behave poorly toward others; repeatedly violate the law, behave irresponsibly and aggressively, disregard the safety of themselves and others. They may participate criminal activities. For diagnosis, the individual must be at least 18 years of age and must have the onset of conduct disorder before 15 years of age.

It is more common in males.

Treatment

- Group therapy
- Limit setting: refusal of relatives to tolerate abuse.
- Mood stabilization medications.

BORDERLINE PERSONALITY DISORDER

In this disorder there is instability in a variety of functions such as mood, behavior, interpersonal relationships and self image. There is unpredictable behavior that is potentially self-damaging.

Management

- Psychotherapy
- Antipsychotic medications

HISTRIONIC (HYSTERICAL) PERSONALITY DISORDER

Individuals with this disorder have extreme emotional lability and constantly attempt to attract attention to themselves through dramatic behavior or ideas. They overreact to minor events, exaggerate emotional outbursts of tearfulness or temper tantrum.
This disorder is more common in females.

Treatment

Psychotherapy

NARCISSISTIC PERSONALITY DISORDER

Individual with this disorder have an overriding sense of entitlement and self-importance along with the lack of understanding and concern for the feelings of others. There is a grandiose sense of self- importance or uniqueness. There are unrealistic fantasies of having unlimited ability, power, wealth, intelligence, creativity, beauty or ideal love. The person seeks and requires constant attention and admiration from others. Person demands special favors without reciprocation.
This disorder is more common in males.

Treatment

Psychotherapy

AVOIDANT PERSONALITY DISORDER

Individual with this order avoids almost all occupational or social relationships because of fear of rejection that is based on feeling of inadequacy.

Management

- Psychotherapy
- Anxiolytic drugs

DEPENDENT PERSONALITY DISORDER

Individuals with disorder show lack of confidence, allow others to assume responsibilities for important decisions, avoid initiating activities independently, feel inadequate and helpless.

Management

Cognitive-behavioral and psychodynamic psychotherapy.

OBSESSIVE – COMPULSIVE PERSONALITY DISORDER

Individuals with this disorder are preoccupied with details and lose a sense of overall goals. They are strict, perfectionistic, over -conscientious and inflexible. The interpersonal relationships are formalized and lack warmth or humor. There is extreme sensitivity to social criticism, and frequent feeling of failure and depression.
It is more common in males.

Management

- Psychotherapy
- Selective serotonin reuptake inhibitors (SSRI)

PASSIVE AGGRESSIVE PERSONALITY DISORDER

The characteristic feature of this disorder is resistance to demands for adequate performance. The person may be aware of aggressive or angry feelings, but feels he or she dare not express them openly. The feelings are therefore expressed indirectly through stubbornness, intentional inefficiency and forgetfulness.

PERSONALITY DISORDERS

Personality	Features
Paranoid	They are mistrustful and suspicious of the motivations and actions of others
Schizoid	They appear uninterested in interacting with others and indifferent to praise or criticism.
Schizotypal	Socially isolated and have odd manners of speech and affect, disturbance in thinking and perception abnormalities such as recurrent illusions.
Antisocial	They repeatedly violate the law, behave irresponsibly and aggressively, disregard the safety of themselves and others
Borderline	They have instability in a variety of functions such as mood, behavior, interpersonal relationships and self image
Narcissistic	They have an overriding sense of entitlement and self-importance along with the lack of understanding and concern for the feelings of others.
Avoidant	They avoid almost all occupational or social relationships because of fear of rejection that is based on feeling of inadequacy.
Dependent	They show lack of confidence
Obsessive – compulsive	They are preoccupied with details and lose a sense of overall goals.
Passive aggressive	They have resistance to demands for adequate performance.
Histrionic	They have extreme emotional lability and they constantly attempt to attract attention to themselves through dramatic behavior or ideas.

ANXIETY DISORDERS

ANXIETY
Anxiety is the state of apprehension (worry), tension, and excessive concern over danger that is either minor in degree or largely unrecognized.

Following conditions are included in anxiety disorder:
- Panic disorder
- Phobic disorder
- Generalized anxiety disorder
- Obsessive-compulsive disorder
- Post-traumatic stress disorder

NORMAL FEAR
Normal fear is a subjective apprehension (worry) and objective physiologic changes, both of which are appropriate in degree and duration to consciously recognized external danger. It prepares for action in the form of strenuous muscular activity (fight and fright). Fear manifests as tachycardia, rapid respiration with hyperventilation, tremor, cold sweat with clammy palms, pallor, dilated pupils and piloerection.

PHOBIA
Phobia is the state of intense, persistent, and irrational fear of some specific object, activity or situation, leading to avoiding behavior.

PANIC DISORDER
Panic disorder consists of discrete episodes of extreme anxiety (panic attacks) that occurs against a background of milder anxiety and nervousness.

Clinical features
The panic attacks are manifested by sudden, intense feelings of apprehension accompanied by the several of the following symptoms: dyspnea, palpitation, chest pain or discomfort, chocking sensation, dizziness, vertigo, parasthesias (tinglin in extremities), hot and cold flashes, sweating faintness and conscious fear of dying.

There is high incidence of mitral valve prolapse in patients of panic disorder, therefore it must be ruled out first with echocardiogram.

Treatment
Anxiolytics: benzodiazepines e.g. alprazolam
Antidepressants: imipramine, SSRI

PHOBIC DISORDERS

Phobia is the state of intense, persistent, and irrational fear of some specific object, activity or situation, leading to avoiding behavior.

Types of phobia

Agoraphobia
It is the fear of street or open places, this term is used for fear of leaving the familiar setting of one's home. It is usually accompanied by other phobias such as fear of crowds, heights, or closed spaces.

Social phobias
It involves excessive fear and avoidance of situations that require possible interaction with other people (such as public speaking).

Simple phobias
These are specific phobias involving neither of the preceding characteristics (such as fear of animals, fear of closed spaces or fear of heights).

Management

- *Systemic desensitization*: gradual exposure to the feared stimuli paired with relaxation training.
- *Flooding:* it involves massive exposure to feared stimuli until anxiety subsides.

GENERALIZED ANXIETY DISORDER

It is an excessive poorly controlled anxiety about life circumstances that continues for more than 6 months. It is often associated with depression.

Management

- Psychotherapy with training of relaxation.
- Antidepressants

OBSESSIVE COMPULSIVE DISORDER

It is characterized by recurrent and persistent obsession or compulsion. Insidious onset occurs during childhood, adolescence, or early adulthood, equally affecting males and females. The symptoms usually wax and wane.

Obsession: unwanted ideas, thoughts, images or impulses.
Compulsion: repetitive and seemingly purposeful actions.

This obsession or compulsion are recognized by the individual as unreasonable and are sufficiently severe to cause marked distress (patient knows that the idea and his act are not logical but he is forced to do that for get rid of anxiety. Attempt to resist leads to more anxiety). For example repeated hand washing with an idea or impulse that harmful germs are present on hands. Impulse to attack someone could be dangerous.

Obsessive-compulsive disorder may be associated with anxiety, depression, feeling of guilt, phobia, and social and occupational problems.

Management

- Behavioral psychotherapy: such as thought stopping techniques, relation training.
- Antidepressants: such as SRRIs (Fluoxetine)

POST-TRAUMATIC STRESS DISORDER

It may be acute in onset (confined to the first 6 months after the traumatic event), chronic (lasting more than 6 months), or delayed (developing later than 6 months after the trauma.
The traumatic event must be of high magnitude such as rape, serious accident, military combat or natural disasters.

Clinical features
Re-experiencing the same traumatic event (as conscious or recurrent dreams). There may be sleep disturbance, guilt about having survived, and difficulty in concentrating.

Management

- Group psychotherapy
- Anxiolytics and antidepressants

SOMATOFORM DISORDERS

These disorders are characterized by somatic (body) symptoms suggestive of physical illness, but without demonstrable organic pathology or known physiologic basis. It means physical symptoms are due to psychological factors. However the development of symptoms is not under voluntary control (in contrast with factitious disorders and deliberate malingering).

HYSTERIA

In hysteria there is a complicated history, beginning before age 30 and extending over a period of several years, of seeking medical attention for a large variety of physical symptoms that are often described in a vague, dramatic or exaggerated manner. Women are more affected than men.

Clinical features

Frequent symptoms are following:

1. *Gastrointestinal:* nausea, abdominal pain, vomiting spells, constipation or diarrhea.
2. *Pain:* back pain, joint pain, pain in extremities and frequent headache, dysuria and perimenstrual pain.
3. *Sexual:* diminished libido, impotence, vaginismus, and genital discomfort.
4. *Psychiatric:* fatigue, depression, and anxiety.

These patients get repeated hospitalizations and multiple surgeries.

Management

- Careful medical and psychiatric examination.
- Find out the psychological distressing factors associated with symptoms.
- Careful prescription of analgesics, anxiolytics and antidepressants.

CONVERSION DISORDER

In this disorder, the individual has sensory or motor symptoms that suggest a general medical condition, however the symptoms are related to stress or conflict. It is more common in females. Symptoms are not intentionally produced.

Clinical features

- *Altered sensation*: anesthesia, paresthesia, partial or complete blindness or deafness.
- *Ataxia or paralysis:* inability to stand or walk, loss of voice.
- *Involuntary movements*: dyskinesia, pseudo-epileptic convulsions.

Management

- Rule out general medical conditions that may be responsible for symptoms.
- Anxiolytics
- Psychotherapy to resolve psychological conflicts.

Note: In hysteria there are symptoms while in conversion disorder signs may be present on examination; caused by intra-psychic conflict.

HYPOCHONDRIASIS

This disorder is characterized by preoccupation with bodily functions and with fear of presumed diseases of various organs. The fear persists in spite of reassurance concerning normal findings from physical examinations and laboratory investigations. Anxiety and depression are commonly associated with this disorder.

Management

- Psychotherapy to resolve underlying psychological conflicts.
- Anxiolytic and anti-depressants are commonly used.

DISSOCIATIVE DISORDERS

In dissociative disorders there are non-organic alterations in the person's consciousness, memory, perception or identity. Individual may forget things that are particularly anxiety provoking, such as events that occurred during periods of threat or stress (e.g. how one managed to escape from a burning building).

The disorders included in this category are:

- Dissociative or psychogenic amnesia
- Dissociative or psychogenic fugue
- Dissociative identity disorder
- Depersonalization disorder

Dissociative or psychogenic amnesia

It is characterized by episodes in which the individual is unable to recall important and often emotionally charged memories such as period during which traumatic incident or experience has occurred.

The types of amnesia (forgetfulness) may be following:

Localized: the individual has amnesia for events that occurred during a specific period of time.

Selective: the individual has amnesia for only specific events that occurred in a circumscribed period of time.

Generalized: the individual has amnesia for all events of his entire life.

Continuous: the individual has amnesia for all events from a particular time to the present.

Systemized: the individual has amnesia for only certain types of information (e.g. for a specific person).

Yade mazi azaab haiy ya Rab
Chheen lay mujh se hafza mera

Management

- Careful evaluation of medical conditions causing amnesia such as head trauma, seizures, cerebrovascular disease, or use of anxiolytic, hypnotics or alcohol.
- Remove the patient from the stressful situation.
- Psychotherapy to resolve underlying emotional stress.

Dissociative or psychogenic fugue

It is a sudden, unexpected travel, accompanied by the inability to remember one's past and by confusion about personal identity, or by the assumption of a new identity.

This disorder involves a combination of amnesia with geographic relocation, temporary or permanent assumption of new identity, and inability to recall one' s previous identity.

A history of acute or chronic stressful events preceding the onset of symptoms may be present.

It must be differentiated from medical conditions such complex partial seizures, dissociative amnesia, dissociative identity disorder, psychosis, factitious disorder and malingering.

Management

- Careful evaluation of medical conditions causing amnesia such as head trauma, seizures, cerebrovascular disease, or use of anxiolytic, hypnotics or alcohol.
- Remove the patient from the stressful situation.
- Psychotherapy to resolve underlying emotional stress.

Dissociative identity disorder

Formerly it was called multiple personality disorder and is characterized by presence o multiple, distinct personalities that recurrentl control the individual's behavior, accompanied b the individual's failure to recall importa personal information.

Management

Psychotherapy

Depersonalization disorder

It is characterized by persistent or recurrent feeling of being detached from one's mental processes or body, accompanied by an intact sense of reality.

Management

Psychotherapy

PSYCHOTIC DISORDERS

Psychosis is a syndrome characterized by gross impairments in the ability to assess reality and behave coherently.

Psychosis is diagnosed if one or more of the following symptoms are present.

Hallucination
These are false sensory perceptions that occur without external stimulation of the relevant organs e.g. listening voices, seeing people when these are not actually present.

Delusions
Delusions are false beliefs that are maintained despite objective evidence and logical arguments are against them e.g. unrealistic belief in one's importance, identity, wealth, fame, power or knowledge. Other example is false belief that others are attacking, harassing, cheating and conspiring against him.

Disorganized speech
It is characterized by incoherence or rambling (e.g. intermittently muttering and shouting unintelligible statements and monologues.

Disorganized behavior
It is characterized by aimless, bizarre, agitated or grossly inappropriate behavior (e.g. wandering alone in the streets dressed inappropriately).

Disorganized motor behavior (catatonia)
It is characterized by marked motor anomalies, including immobility, posturing, stereotyped movements, echolalia and echoparaxia.

SCHIZOPHRENIA

Schizophrenia (shizofrenia) is a psychiatric illness characterized by psychosis and disintegration of abilities to think logically and maintain normal social behavior. Common people say it madness. It equally affects males and females. Most common between 15-35 years of age. Increased prevalence in lower socioeconomic group. There is 10% prevalence in first-degree biologic relatives.

Symptoms
Certain symptoms of schizophrenia are classified as either positive or negative. Positive symptoms are hallucinations and delusions. Negative symptoms are lack of emotions, lack of motivation, poverty of speech, disinterest and social withdrawal.

For diagnosis two or more of the following symptoms should be present for <u>at least 6 month</u> duration:

1. Hallucinations
2. Delusions
3. Disorganized speech
4. Grossly disorganized or catatonic behavior
5. Negative symptoms e.g. affective flattening, alogia or ovolition.

SYMPTOMS OF SCHIZOPHRENIA

Symptoms	Examples
Positive symptoms	• Hallucinations • Delusions
Negative symptoms	• Affective flattening (flat, blunted, labile, inappropriate emotional response) • Avolition (lack of motivation) • Alogia (poverty of speech) • Social withdrawal
Disorganized symptoms	• Illogical or incoherent speech • Aimless or peculiar motor behavior
Cognitive symptoms	• Impaired attention • Impaired ability to plan, organize. • Impaired memory
Other associated symptoms	• Sleep disturbance • Depressed mood or unstable mood • Substance abuse

TYPES OF SCHIZOPHRENIA

Paranoid schizophrenia
Hallucinations or delusions are present, but there are no catatonic symptoms.

Catatonic
It is characterized by stupor, mutism, rigidity, purposeless excitement, echolalia.

Disorganized
Grossly disorganized behavior, flat or grossly inappropriate affect.

Undifferentiated
Characterized by prominent delusions, hallucinations or grossly disorganized behavior but does not meet the criteria for paranoid, catatonic or disorganized type.

Residual type
Absence of prominent delusions, hallucinations or grossly disorganized behavior. There is continuing evidence of the disturbance through two or more of the residual symptoms.

DIFFERENTIAL DIAGNOSIS

- Medical disorders: substance abuse, encephalitis, SLE, complex partial seizures.
- Schizophreniform disorder: symptoms similar to schizophrenia but last for less than 6 months.
- Brief psychotic disorder
- Mania, depression
- Schizoaffective disorder
- Delusional disorder
- Mental retardation

TREATMENT

Antipsychotic medications: Chlorpromazine, haloperidol, risperidone, clozapine are commonly used.

Mode of action
Mode of action of antipsychotic drugs is dopamine receptor antagonism in brain. Some newer drugs block serotonin receptors in brain.

Side effects
1. Hypotension, anticholinergic symptoms
2. Movement disorders such as:
   - Extrapyramidal syndromes (EPS) presenting as dystonia, bradykinesia, akathisia (restlessness).
   - Tardive dyskinesia: choreoathetosis and other involuntary movements, initially involving tongue or fingers and later trunk also.
   - Neuroleptic malignant syndrome (NMS) characterized by muscular rigidity, hyperthermia, autonomic instability, and delirium.
3. *Other side effects*
   - Lenticular opacities.
   - Gynaecomastia, galactorrhea and amenorrhea
   - Social rehabilitation and family therapy.

PROGNOSIS

About 1/3 patients lead somewhat normal lives, 1/3 continue to experience significant symptoms but can function within society, remaining 1/3 are markedly impaired and require frequent hospitalization.

FEATURES SUGGESTING PROGNOSIS IN SCHIZOPHRENIA

Good prognosis	Poor prognosis
• Later onset • Acute onset • Prominent mood symptoms • Family history of mood disorder • Supportive family or friends • Prominent positive symptoms • Short active phase • Few relapses	• Younger onset • Insidious onset • Affectual blunting • Family history of schizophrenia • Absence of social support • Prominent negative symptoms • Prolonged active phase • Multiple relapses

SCHIZOPHRENIFORM DISORDER

It is characterized by clinical picture of schizophrenia with a duration of less than 6 months. About 1/3 to ½ patients of schizophreniform disorder develop scizophrenia.

SCHIZOAFFECTIVE DISORDER

It is characterized by a history of prominent mood episodes with concurrent psychosis. The psychosis persists even when the mood episodes remit

HALLUCINATION

Hallucinations are defined as "an apparent perception of an external object when no such object is present". Hallucinations are false or distorted sensory experiences that appear to be real perceptions. These sensory impressions are generated by the mind rather than by any external stimuli, and may be seen, heard, felt, and even smelled or tasted. The hallucinatory experience has a wide range of etiologies like neurological insult, seizure and sleep disorders, drug reactions, substance abuse, grief, stress, as well as metabolic, endocrine and infectious diseases.

A hallucination occurs when environmental, emotional, or physical factors such as stress, medication, extreme fatigue, or mental illness cause the mechanism within the brain that helps to distinguish conscious perceptions from internal, memory-based perceptions to misfire. As a result, hallucinations occur during periods of consciousness. They can appear in the form of visions, voices or sounds, tactile feelings, smells, or tastes. Patients suffering from dementia and psychotic disorders such as schizophrenia frequently experience hallucinations. Hallucinations can also occur in patients who are not mentally ill as a result of stress overload or exhaustion, or may be intentionally induced through the use of drugs, meditation, or sensory deprivation.

MORE COMMON CAUSES

Drugs

- Drug intoxication
- LSD intoxication
- Marijuana intoxication
- Cannabis

Psychotic disorders

- Schizophrenia
- Schizotypal personality disorder
- Schizoid personality disorder
- Brief psychotic disorder
- Bipolar disorder - previously known as "manic-depressive disorder"
- Mania - if causing psychosis
- Drug-induced psychoses

Less common causes

- Grief - will rarely cause hallucinations in very severe grief.
- Postpartum psychosis
- Korsakoff's psychosis

Alcohol abuses

- Alcohol poisoning (type of Poisoning)
- Delirium tremens
- Alcoholic hallucinosis

Physical medical conditions

- Extreme physical stress
- High fever (see Fever)
- Dehydration
- Extreme fatigue (see Fatigue)
- Kidney failure

Brain disorders

- Dementia - see causes of dementia
- Delirium - see causes of delirium
- Confusion
- Alzheimer's disease
- Stroke
- Migraine
- Brain tumor
- Seizures
- Temporal lobe epilepsy (type of Epilepsy) - sometimes hallucations of smell or taste.

Eye disorders - may cause various visual effects which might be described as visual hallucinations.

- Cataracts
- Glaucoma
- Retinal ischemia
- Optic nerve lesion

TYPES OF HALLUCINATIONS

- **An auditory hallucination** is an hallucination involving the sense of hearing. Called also paracusia and paracusis.
- **A gustatory hallucination** is an hallucination involving the sense of taste.
- **Olfactory hallucination** is an hallucination involving the sense of smell.
- **Somatic hallucination** is an hallucination involving the perception of a physical experience occurring with the body.
- **Tactile hallucination** is an hallucination involving the sense of touch.

- **Visual hallucination** is an hallucination involving the sense of sight.
- **A hypnagogic hallucination** is a vivid dreamlike hallucination at the onset of sleep.
- **Hypnopompic hallucination** is a vivid dreamlike hallucination on awakening.
- **Kinesthetic hallucination** is an hallucination involving the sense of bodily movement.
- **Lilliputian hallucination** is an hallucination in which things, people, or animals seem smaller than they would be in reality.

Causes of visual hallucinations
- Migraine
- Seizures
- Visual loss (*ie,* release hallucinations)
- Neurodegenerative disorders e.g. Parkinson's disease and Alzheimer's disease
- Midbrain injury
- Alcohol
- Drug effects
- Narcolepsy
- Post-traumatic stress disorder
- Psychosis

DELUSIONAL DISORDER

Delusional disorder is characterized by the condition in which the primary or sole manifestation is a delusion that is fixed and unshakable. Unlike schizophrenia patients with delusional disorder are not overtly bizarre and their thoughts are generally organized.

Delusions are false beliefs that are maintained despite objective evidence and logical arguments are against them e.g. unrealistic belief in one's importance, identity, wealth, fame, power or knowledge. Other example is false belief that others are attacking, harassing, cheating and conspiring against him.

TYPES OF DELUSIONAL DISORDER

Erotomanic type: characterized by delusions of having a special relationship with another person, often-famous person.

Grandiose type: characterized by delusions of power, wealth, or other inflated status.

Jealous type: characterized by delusions of infidelity of sexual partner.

Persecutory type: characterized by delusions of being persecuted in some way.

Somatic type: characterized by delusions of having a physical problem or condition.

Mixed type: characterized by delusions of more than one type.

TREATMENT
- Antipsychotic medication.
- Anxiolytic medication.
- Supportive and cognitive psychotherapy.

BRIEF PSYCHOTIC DISORDER

Brief psychotic disorder is characterized by the sudden onset of brief psychotic episodes.
- The onset may occur in response to severe stress, during the postpartum period or without obvious relationship to environmental events.
- Episodes may resolve within 1 month.
- **Treatment**: antipsychotic medications.

PSYCHOSIS DUE TO GENERAL MEDICAL CONDITIONS

Psychosis may be the one of the feature of medical condition, therefore always rule out possible medical disorder before labeling the patient as psychiatric patient.

CAUSES
- **Cerebrovascular:** stroke, vascular insufficiency.
- **CNS lesions**: head trauma,tumor, radiation, and infections.
- **Metabolic:** electrolyte disturbance, hypoglycemia, hypoxia, and hypercarbia.
- **Endocrine:** disorders of thyroid, parathyroid and adrenal glands.
- **Autoimmune**: SLE
- **CNS tumors:**
- **Neurodegenerative disorders:** Parkinson disease, Huntington disease.

TREATMENT
Correction of underlying cause

CAUSES OF DRUG INDUCED PSYCHOSIS

Alcohol. Amphetamine, cannabis, cocaine, hallucinogens, inhalants, opiods, phencyclidine, sedatives, hypnotics, anxiolytics, digitalis, cimetidine, amantadine, and steroids.

MOOD DISORDERS

Mood is the sustained emotional tone. There are two conditions included in mood disorders:

1. Major depression
2. Mania

DEPRESSION

Depression is a mental state of excessive sadness characterized by persistently low mood, loss of pleasure and interest.

Unhappiness is one of the most common psychiatric complaints and unlike normal emotional experiences of sadness, loss, or passing mood states, major depression is persistent and can significantly interfere with an individual's thoughts, behavior, mood, activity, and physical health.

Diagnostic criteria for major depression

Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either: (1) depressed mood or (2) loss of interest or pleasure.

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful). Note: In children and adolescents, can be irritable mood.
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)
3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. Note: In children, consider failure to make expected weight gains.
4. Insomnia or hypersomnia nearly every day
5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down)
6. Fatigue or loss of energy nearly every day
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

Very severe depression may be accompanied by psychotic features such as delusions, hallucinations, grossly bizarre behavior, or stupor with mutism and unresponsiveness.

Laboratory findings:

- Increased REM sleep time
- Decreased serotonin in blood and CSF
- Relative dexamethasone nonsuppression

Symptoms of depression

- Persistently sad or irritable mood
- Pronounced changes in sleep, appetite, and energy
- Difficulty thinking, concentrating, and remembering
- Physical slowing or agitation
- Lack of interest in or pleasure from activities that were once enjoyed
- Feelings of guilt, worthlessness, hopelessness, and emptiness
- Recurrent thoughts of death or suicide
- Persistent physical symptoms that do not respond to treatment, such as headaches, digestive disorders, and chronic pain

Causes of depression

There is no single cause of major depression. Psychological, biological, and environmental factors may all contribute to its development.

Whatever the specific causes of depression, scientific research has firmly established that major depression is a biological brain disorder.

Norepinephrine, serotonin, and dopamine are three neurotransmitters (chemical messengers that transmit electrical signals between brain cells) thought to be involved with major depression. It is believed that if there is a chemical imbalance in these neurotransmitters, then clinical states of depression result. Antidepressant medications work by increasing the availability of neurotransmitters or by changing the sensitivity of the receptors for these chemical messengers.

There is also evidence of a genetic predisposition to major depression. There is an increased risk for developing depression when there is a family history of the illness. Not everyone with a genetic predisposition develops depression, but some people probably have a biological make-up that leaves them particularly vulnerable to developing depression. Life events, such as the death of a loved one, a major loss or change, chronic stress, and alcohol and drug abuse, may trigger episodes of depression. Some illnesses such as heart disease and cancer and some medications may also trigger depressive episodes. It is also important to note that many depressive episodes occur spontaneously and are not triggered by a life crisis, physical illness, or other risks.

TREATMENT

There are three basic types of treatment for depression: medications, psychotherapy, and electroconvulsive therapy (ECT). They may be used singly or in combination.

MEDICATION.

The first antidepressant medications were introduced in the 1950s. Research has shown that imbalances in neurotransmitters like serotonin, dopamine, and norepinephrine can be corrected with antidepressants. Four groups of antidepressant medications are most often prescribed for depression:

Tricyclic antidepressants (TCAs)

Still widely used for severe depression. TCAs elevate mood in depressed individuals; re-establish their normal sleep, appetite and energy level , but it often takes three to four weeks for an individual to respond.

These medications include:

- Amitriptyline (Tryptanol)
- Imipramine (Tofranil)
- Clomipramine (Clomfranil)
- Nortriptyline (Motival)
- Dothiepin (Prothiaden)

Tetracyclic antidepressants

- Maprotiline (Ludomil)
- Mianserin (Lantanon)

Side effects

Dry mouth, constipation, bladder problems, sexual problems, blurred vision, dizziness, drowsiness, skin rash, and weight gain or loss.

Selective serotonin reuptake inhibitors (SSRIs)

They act specifically on the neurotransmitter serotonin. In general SSRIs cause fewer side effects than TCAs and MAOIs. These medications include:

- Fluoxetine (Prozac)
- Sertraline (Zoloft)
- Paroxetine (Seroxat)
- Citalopram (Cipram)
- Escitalopram (Cipralex).

Serotonin and norepinephrine reuptake inhibitors (SNRIs) – useful as first-line treatments in people taking an antidepressant for the first time and for people who have not responded to other medications. In general SNRIs cause fewer side effects than TCAs and MAOIs. These medications include:

- Venlafaxine (Effexor)

Side effects of SSRIs and SNRIs

Nausea, nervousness, insomnia, diarrhea, rash, agitation, or sexual side effects (problems with arousal or orgasm).

Monoamine oxidase inhibitors (MAOIs)

They are often effective in individuals who do not respond to other medications or who have "atypical" depressions with marked anxiety, excessive sleeping, irritability, hypochondria, or phobic characteristics. These medications include:

- Moclobemide (Aurorix)

Side effects

Individuals taking MAOIs may have to be careful about eating certain smoked, fermented, or pickled foods, drinking certain beverages, or taking some medications because they can cause severe high blood pressure in combination with the medication. A range of other, less serious side effects occur including weight gain, constipation, dry mouth, dizziness, headache, drowsiness, insomnia, and sexual side effects (problems with arousal or satisfaction).

PSYCHOTHERAPY

There are several types of psychotherapy that have been shown to be effective for depression including cognitive-behavioral therapy (CBT) and interpersonal therapy (IPT). Mild to moderate depression can often be treated successfully with either of these therapies used alone. However, severe depression appears more likely to respond to a combination of psychotherapy and medication.

Cognitive-behavioral therapy (CBT) – helps to change the negative thinking and unsatisfying behavior associated with depression, while teaching people how to unlearn the behavioral patterns that contribute to their illness.

Interpersonal therapy (IPT) – focuses on improving troubled personal relationships and on adapting to new life roles that may have been associated with a person's depression.

ELECTROCONVULSIVE THERAPY (ECT)

Electroconvulsive therapy (ECT) is a treatment for severe mental illness in which a brief application of electric stimulus is used to produce a generalized seizure. ECT is a highly effective treatment for severe depressive episodes. In situations where medication, psychotherapy, and a combination of the two prove ineffective, or work too slowly to relieve severe symptoms such as psychosis or thoughts of suicide, ECT may be considered. ECT may also be considered for those who for one reason or another cannot take antidepressant medications such as in patients with severe depression or psychosis during the first trimester of pregnancy.

Indications of ECT

- The patient is unresponsive to adequate trials of antidepressants or there are contraindications to use of these agents.
- The patient's immediate risk for suicide is too great to wait for response to antidepressants.
- Urgent need for rapid recovery

Side effects

Medical

During the few minutes following the stimulus, profound and potentially dangerous systemic changes occur. First, there may be transient hypotension from bradycardia caused by central vagal stimulation. This may be followed by sinus tachycardia and also sympathetic hyperactivity that leads to a rise in blood pressure, a response that may be more severe in patients with essential hypertension. Intracranial pressure increases during the seizure. Additionally, cardiac arrhythmias during this time are not uncommon (but usually subside without sequelae). Thus, certain patient groups that would be adversely affected by these manifestations are at increased risk.

CNS

There are two categories of central nervous system effects: The immediate consequences of the ECT seizure and the more enduring effects, both of which are affected by the treatment course. Immediately after awakening from the treatment, the patient experiences confusion, transient memory loss, and headache. The time it takes to recover clear consciousness, which may be from minutes to several hours, varies depending on individual differences in response, the type of ECT administered, the spacing and number of treatments given, and the age of the patient.

Contraindications for ECT

- Increased intracranial pressure
- Space-occupying lesions in the brain
- Recent history of myocardial infarction
- Large aneurysms

MANIA

Mania is a state of abnormal mood that is predominantly euphoric and irritable. There may be rapid shifts to anger or even to short-lived spells of depression, with tearfulness, suicide threats and other depressive symptoms.

Clinical features

- Excessive spending of money
- Excessive gambling
- Hypersexuality
- Low frustration tolerance
- Increased libido
- Weight loss, anorexia
- Insomnia, excessive energy
- Increased psychomotor activity or restlessness
- Pressured speech
- Flight of ideas
- Grandiosity
- Marked impairment in occupational functioning

HYPOMANIA

Hypomania is a clinical state that is similar to mania but less severe.

BIPOLAR DISORDER I

It is characterized by history of manic or mixed episodes (both manic and depressive) during the course of disorder.

Treatment

- *Lithium:* indicated in mania, bipolar disorder and in major depression as an adjunctive treatment. Side effects are, nausea, vomiting, diarrhea, tremor, diabetes insipidus, hypothyroidism, acne, weight gain and teratogenicity causing ASD.
- Antidepressants with lithium
- Antipsychotics if there is psychosis
- ECT used when severe mood episodes do not respond to medication.

BIPOLAR II DISORDER

It is characterized by major depressive episodes and at least one hypomanic episode but no manic episode.

Treatment

Similar to the treatment of bipolar I disorder.

COGNITIVE DISORDERS

Organic mental disorders or cognitive disorders (due to brain dysfunction) are classified into 3 groups:

1. Delirium, dementia and amnestic disorders.
2. Mental disorders due to general medical conditions
3. Substance related disorders

Disturbance in cognition may be memory impairment, aphasia, apraxia (loss of learnt skills), agnosia (failure to recognize people or objects), or disturbance in executive functions such as ability to think, plan and monitor.

DELIRIUM

Delirium is an acute reversible mental disorder characterized by confusion and some impairment of consciousness; generally associated with emotional lability, hallucinations or illusions, and inappropriate, impulsive, irrational, or violent behavior. It is often caused by acute metabolic problems or substance intoxication.

Causes

General medical conditions

Infections, metabolic disorders, hepatic or renal failure, seizures, and head injury.

Substance induced conditions

Drug intoxication, drug withdrawal

Treatment

- Treatment of underlying cause
- Protection of patient
- Antipsychotics

DEMENTIA

It is a medical disorder characterized by general impairment in intellectual functioning, usually because of underlying progressive degenerative brain disease.

Clinical features

- Memory disturbances
- Acalculia (difficulty with calculations)
- Alteration in mood and affect
- Impairment in judgment
- Reduced facility with language
- Disturbance in orientation.

CAUSES OF DEMENTIA	
Degenerative brain disorders Alzheimer disease Pick's disease Parkinson's disease Wilson disease Progressive supranuclear palsy	**Drugs and toxins** Alcohol Heavy metals Carbon monoxide poisoning Medications Irradiation
Chronic infections Syphilis Creutzfeldt-Jakob-disease AIDS dementia complex	**Cardiac / vascular** Myocardial infarction Lacunar brain infarctions
Trauma Hematoma Post-traumatic dementia	**Tumors** Primary brain tumors Metastatic tumors
Congenital/hereditary Huntington's disease Leukodystrophy	**Physiological** Epilepsy Normal pressure hydrocephalus
Metabolic Vitamin deficiency Chronic anoxia Chronic metabolic disturbance Chronic endocrinopathies	**Demyelinating** Multiple sclerosis

Treatment

- Nursing care
- Psychological supportive therapy
- Antipsychotics in low doses for agitation.

AMNESTIC DISORDER

Amnestic disorder is characterized by impaired recent, short term and long term memory attributed to specific organic etiology i.e. drug or medical disease. Patient is normal in other areas of cognition.

Causes

Systemic medical conditions

- Thiamine deficiency (Korsakoff's syndrome)
- Hypoglycemia

Primary brain conditions

- Seizures
- Head trauma
- Cerebrovascular disease
- Encephalitis
- Hypoxia
- ECT
- Multiple sclerosis

Substances

- Alcohol
- Benzodiazepine

SUBSTANCE ABUSE

Substance abuse denotes the pathologic use, repeatedly over a period of time, of any substance that affects the central nervous system, in such a manner that behavior interferes with the person's normal social or occupational functioning. For diagnosis all of the three factors should be present:

1. Pattern of pathological use such as inability to reduce or terminate use of the substance.
2. Duration of at least 1 month.
3. Impairment in social or occupational functioning.

Disorders related to substance abuse (alcohol or drugs) may be the following:

- Substance dependence
- Substance-induced disorders

Substance dependence (addiction)

Substance dependence is characterized by substance tolerance and withdrawal syndrome on discontinuation.

<u>*Tolerance:*</u> a state of cellular adaptation in which increasing amounts of substance are required to produce the same intoxicating effects, or in which significantly decreasing effects are obtained from the same amount.

<u>*Withdrawal syndrome:*</u> also called abstinence syndrome that develops following soon after the abrupt termination of or substantial reduction in the amount of the substance used.

Treatment

There are 4 phases in the management of drug abuse and addiction:

1. *Prevention:* use social pressure against use of drug.
2. *Detoxification:* give medications and supportive measures to minimize effects of the drug and of its withdrawal.
3. *Substitution therapy:* with related drugs which may be temporary such as use of methadone in place of heroin.
4. Antianxiety or antidepressant drugs.

COMMONLY ABUSED SUBSTANCES
- Nicotine
- Alcohol
- Marijuana
- Inhalants such as paint thinner, nitrous oxide
- Cocaine
- Amphetamine
- Heroin
- Hallocinogen e.g. LSD
- Benzodiazepine and other sedatives, hypnotics
- Anabolic steroids
- Antihistamines

Substance induced disorders

Substance intoxication: substance specific syndrome caused by recent ingestion of or exposure to a substance.

Substance withdrawal: substance specific maladaptive behavioral change caused by cessation of or reduction in heavy and prolonged substance use.

EATING DISORDERS

ANOREXIA NERVOSA

It is a serious and potentially fatal condition characterized by a disturbed body image and self-imposed severe dietary limitation, usually resulting in serious malnutrition.

Prevalence: 0.5-1% of adolescent girls, usually associated with stressful life event, male to female ratio 1:10-20.

Diagnostic features
- There is intense fear of becoming obese, continuing despite weight loss.
- There is disturbance of body image- feeling fat even emaciated.
- Weight loss of 25% from either original weight or projected weight on growth charts.
- No known physical cause of weight loss.
- Refusal to maintain weight at normal.

Treatment
- Hospitalization, correction of metabolic disturbance.
- Behavioral therapy
- Family therapy
- Antidepressants

BULIMIA NERVOSA

Bulimia nervosa is characterized by frequent binge eating and purging and a self- image that is unduly influenced by weight. It occurs usually in young females. There are repeated attempts to lose weight. Weight is usually normal or slightly increased in bulimia nervosa.

Treatment
- Cognitive and behavioral treatments
- Antidepressants especially SSRIs
- Psychotherapy.

SUICIDE

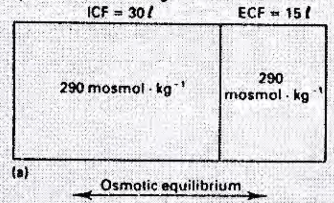
Risk factors

1. Age: high risk in adolescence, early childhood and also in age group 40-50.
2. Sex: men commit successful suicide more often than women. Women attempt suicide more often than men. Men often use more violent methods than women.
3. Recent attempt or gesture.
4. Possession of gun, pills.
5. Intent to dye
6. Psychological disorders: depression, psychosis, substance abuse.
7. Medical illness: chronic terminal, painful, debilitating disease such as malignancy with pain.
8. Recent stresses: loss of spouse, break of engagement, refusal from parents to allow marry to some loving person (common in our society).
9. Living situation: urban, isolated, extreme of social class.
10. Marital status: separated, divorced, widowed, single.
11. Professional status: poor, unemployed, or professionals.
12. Family history: early parental loss, family history of mood disorder.
13. Mental status: command auditory hallucinations, hopelessness, suicide ideation.
14. People who disclose their ideation of suicide have increased risk of suicide.
15. Previously unsuccessful attempts.
16. Suicide by close relative.

Fluid & Electrolytes 13

BODY FLUID VOLUME AND DISTRIBUTION

Water is the chief component of the body, accounting for 45-80% of the body weight. The percentage varies with age, sex and body build.



- The body of healthy 75kg male contains approximately 45 liters of water.
- Two thirds (30 liters) is intracellular fluid (ICF)
- One third (15 litre) is extracellular fluid (ECF) which is divided between interstitial fluid (10 liters) and the vascular compartment (5 liters).

COMPOSITION OF BODY FLUIDS

Table 10.2 Electrolyte composition of intracellular and extracellular fluids.

	Plasma (mmol·L⁻¹)	Interstitial fluid (mmol·L⁻¹)	Intracellular fluid (mmol L⁻¹)
Na^+	142	144	10
K^+	4	4	160
Ca^{2+}	2.5	1.25	1.5
Mg^{2+}	1.0	0.5	13
Cl^-	102	114	2
HCO_3^-	26	30	8
PO_4^{2-}	1.0	1.0	57
SO_4^{2-}	0.5	0.5	10
Organic acid	6	5	
Protein	16	0	55

Factors controlling volume & composition

1. Osmoreceptors — principally in hypothalamus
2. Volume receptors — in capacitance vessels close to the heart
3. Renin-angiotensin system.

An increase in intracellular osmolality - for example after water deprivation stimulates both thirst and release of antidiuretic hormone (ADH) from posterior pituitary. Thirst stimulates increased water intake while ADH increases the reabsorption of water from the tubular fluid by its action on the distal tubules of the kidney, this causes a reduction in the urine output. The increased intake of water and reduced urinary excretion result in a net gain of water that returns body fluid osmolality to normal. A decrease in intracellular osmolality in the osmo receptors has the reverse effect.

Control of body sodium and extra cellular fluid

Sodium and its accompanying anions, principally chloride and bicarbonate are the main extracellular electrolytes. They are main determinants of plasma osmolality and, through osmo receptors, they control the fluid balance. It is the amount of sodium in extracellular fluid that determines the volume of ECF; control of the volume of ECF is thus achieved by controlling the amount of sodium in the ECF.

CLINICAL ASSESSMENT OF WATER AND ELECTROLYTE BALANCE

Average daily intake

1) Sodium: 100-250 mmol
2) Potassium: 40-120 mmol
3) Water: 50-2500 ml

HISTORY

History should be taken to define circumstances that might lead to fluid and electrolyte imbalance such as vomiting, diarrhoea or polyuria.

Possible losses from the gut

Table 10.3 Average concentrations and potential daily losses of water and electrolytes from the gut.

	Na^+ ($mmol \cdot L^{-1}$)	K^+ ($mmol \cdot L^{-1}$)	Cl^- ($mmol \cdot L^{-1}$)	Volume (ml per 24 h)
Stomach	50	10	110	2500
Small intestine:				
Recent ileostomy	120	5	110	1500
Adapted ileostomy	50	4	25	500
Bile	140	5	105	500
Pancreatic juice	140	5	60	2000
Diarrhoea	130	10–15	95	1000–2000+

PHYSICAL EXAMINATION

1) Features of fluid depletion (dehydration)

CLINICAL FEATURES OF SODIUM AND WATER DEPLETION

Mild
Approximate deficit 1–2 l in 65-kg adult (2.5–5 mmol/kg BW Na^+)
Lassitude, light headedness, postural hypotension

Moderate
Approximate deficit 2–4.5 l in 65-kg adult (5–11 mmol/kg BW Na^+)
Lassitude, giddiness, nausea, headache
Reduced skin elasticity
Tachycardia, peripheral vasoconstriction, systolic BP reduced but rarely < 90, marked postural hypotension
In larger deficits: oliguria, blood urea raised

Severe
Approximate deficit 4.5–9 l in 65-kg adult (11–22 mmol/kg BW Na^+)
Apathy, weakness, confusion, coma
Reduced skin elasticity
Peripheral circulatory failure, systolic BP < 90
Oliguria, blood urea raised
Plasma [Na^+] usually low*

* When plasma [Na^+] low muscle cramps, mental confusion common

2) Features of fluid overload

a) Sacral or symmetrical peripheral oedema
b) Basal lung crepitations

Daily weight chart and intake output charts are necessary in patients with water & electrolyte imbalance in hospital.

INVESTIGATIONS

1) An abnormally high hemoglobin or hematocrit suggests fluid depletion.
2) Serum electrolytes.
3) 24-hour urinary sodium excretion: In the presence of frank ECF depletion a urinary sodium of less than 10 mmol/l excludes renal loss whereas a value of more than 20m mol/l indicates impairment of renal conservation.

Causes of fluid and electrolyte disturbances.

Losses

Gut
Vomiting
Diarrhoea
Fistula or 'ostomies'
Paralytic ileus

Kidneys
Diuretic therapy
Polyuria
- Post-obstructive
- Post-acute tubular necrosis
- Severe renal failure
- Hypokalaemia
- Lithium therapy
- Hypercalcaemia

Diabetes mellitus
Diabetes insipidus
Hypoadrenalism

Reduced intake

Loss of thirst mechanism
Unconscious/confused states
Hypothalamic lesion (rare)

Lack of access to water
Unconscious/confused states
Bedridden
Infants

Inappropriate/inadequate intake
Hospitalized patients, especially on i.v. regimens

Fluid retention

Heart failure
Hypoproteinaemia, e.g. cirrhosis, nephrotic syndrome
Oliguric renal failure
Cirrhosis
Excessive fluid replacement
Inappropriate ADH secretion
Idiopathic oedema

SODIUM AND WATER DEPLETION

Causes of mixed sodium and water depletion

oss from alimentary tract	*External loss* Vomiting Aspiration of GI contents Fistulae Diarrhoea Villous adenoma of large bowel *Sequestration of fluid in bowel* Ileus Intestinal obstruction
oss in urine	*Extrarenal factors acting on kidney* Osmotic diuresis Diabetes mellitus Mannitol Diuretics Metabolic acidosis Adrenocortical insufficiency *Renal disease* Diuretic phase acute tubular necrosis Post obstructive diuresis Chronic renal insufficiency Proximal renal tubular acidosis Medullary cystic disease Congenital polycystic disease Chronic interstitial nephritis
oss in sweat	Fevers, hot environment
oss in exudates and ansudates, 'third' space losses'	*Loss from body surfaces* Burns Extensive dermatitis *Loss into body cavities or soft tissues* Ascites Peritonitis Acute pancreatitis Rhabdomyolysis Inferior vena caval thrombosis

Clinical features

Dry tongue, low intraocular pressure & inelastic skin.

Detailed features are already given in table.

Management

GUIDELINES FOR REPLACEMENT OF SODIUM AND WATER DEFICITS IN A 65-KG ADULT

The size of deficit is assessed from the history and clinical features

Mild depletion

Slow sodium 6-10 tabs/day (60-100 mmol NaCl) in divided doses, Water 2-3 l/day — 2-3 days

or

0.9% NaCl solution i.v. 1-2 l — 24 hours

Moderate depletion

0.9% NaCl solution i.v. 2-4 l — 1-2 days

Severe depletion

0.9% NaCl solution i.v. 4-9 l. The first 2-3 l to be infused rapidly over 2-3 hours — 2 days

Indications of circulatory overload during fluid administration

Rapid increase JVP, CVP or pulmonary capillary wedge pressure

Crackles at lung bases

Indications of correction of deficit

Normal pulse, BP, urine output

Restoration skin elasticity

Plasma [Na^+] in reference range, blood urea falling

Coexisting metabolic acidosis

Treat if indicated (p. 224) by giving 1/3-1/2 of total Na^+ requirement as 1.26% $NaHCO_3$ solution

Coexisting K^+ or Mg deficit

Add KCl (p. 218) or $MgCl_2$ (p. 221) to i.v. fluid when circulation and urine output restored

Maintenance therapy

Measure or estimate daily losses Na^+ and water

Replace losses daily

Weigh daily, examine for evidence fluid depletion or overload, measure plasma electrolytes daily, adjust therapy accordingly

Intravenous fluids in general use for fluid and electrolyte disturbances.

	Na^+ ($mmol \cdot L^{-1}$)	K^+ ($mmol \cdot L^{-1}$)	HCO_3^- or equivalent ($mmol \cdot L^{-1}$)	Cl^- ($mmol \cdot L^{-1}$)	Ca^{2+} ($mmol \cdot L^{-1}$)	Indication (see footnotes)
Normal plasma values	142	4.5	26	103	2.5	
Sodium chloride 0.9% ('normal saline')	150	—	—	150	—	1
Sodium chloride 0.18% + glucose 4% ('1/5 normal saline')	30	—	—	30	—	2
Glucose 5%	—	—	—	—	—	3
Sodium bicarbonate 1.26%	150	—	150	—	—	4
Sodium bicarbonate 8.4%	1000	—	1000	—	—	5
Compound sodium lactate (Hartmann's)	131	5	29	111	2	6

PRIMARY WATER DEPLETION

Pure or predominant water depletion is the condition when there is clinical evidence of fluid deficit but serum sodium value within normal range 135-150mmol/l.

Aetiology

1. Reduced intake
2. Increased loss from skin: due to fever & hot environment
3. Increased loss from respiratory tract: due to hyperventilation & fever.
4. Polyuria.

Consequences of water depletion

- As water is lost ECF becomes hypertonic and the plasma sodium rises. Water then migrates from cells until osmotic equilibrium is re-established, resulting in intracellular dehydration.
- Stimulation of renin-angiotenison occurs which increases reabsorption of sodium and chloride and excretion of potassium (to prevent fluid loss). Retained (Na^+ and cl^- further increase ECF tonicity, thereby facilitating transfer of water from cells.

Clinical features

Causes of pure or predominant water depletion

Reduced intake	Water unavailable Infants, aged, coma, apathy, depression Inability to swallow, nausea Primary hypodipsia
Increased loss from skin	Fever, hyperthyroidism Hot environment
Increased loss from respiratory tract	Hyperventilation, fever High altitudes
Increased loss in urine due to marked impairment of urinary concentrating mechanism	*ADH deficiency* Diabetes insipidus *Renal tubular lesions* Nephrogenic diabetes insipidus Hypercalcaemia, K^+ depletion Chronic interstitial nephritis Amyloidosis, obstructive uropathy Medullary cystic disease *Solute diuresis* Diabetes mellitus Tube } feeds with high solute Parenteral } concentration Infants feeds wrongly made up

Management

GUIDELINES FOR REPLACEMENT OF WATER DEFICITS IN A 65-KG ADULT

The size of deficit is assessed from the history and clinical features.

Mild depletion

Water 2 l by mouth	6-12 hours
or	
5% glucose solution i.v. 2 l	12 hours

Moderate depletion

5% glucose solution i.v. 2-4 l	24 hours

Severe depletion

0.9% NaCl solution i.v. 1 l	1 hour
5% dextrose solution i.v. 3 l	24 hours
5% dextrose solution i.v. 4 l or equivalent water by mouth	24-48 hours
5% dextrose solution i.v. or water by mouth to restore remaining deficit	48-96 hours

If plasma [K^+] low give KCl by mouth or in i.v. fluids (p. 218) once urine output > 500 ml/day

Indications of correction of deficit

Restoration of circulation
Relief of thirst
Urine output > 1500 ml/24 hours in those previously oliguric
Plasma [Na^+] in reference range

Maintenance therapy

Water 2.5 l/24 hours by mouth, more if polyuria or high fever present (some or all may be given as 5% glucose solution i.v.).
Treat diabetes insipidus if present

WATER EXCESS

Aetiology

Conditions associated with impaired excretion of water

Renal	Acute renal failure Chronic renal failure Nephrotic syndrome
Endocrine	SIADH[1] (Table 6.5) Primary or secondary adrenocortical insufficiency Hypothyroidism
Hepatic	Liver failure Hepatic cirrhosis
Congestive cardiac failure	
Extracellular fluid volume depletion	
Drugs	Diuretics which impair urinary dilution (frusemide, bumetanide, metolazone, benzothiadiazines) Drugs thought to induce SIADH (Table 6.5)

[1]Secretion of ADH from the posterior pituitary in the absence of recognised osmotic or haemodynamic stimuli or secretion of ADH or ADH-like peptides by a malignant neoplasm.

Clinical features

Excessive water in the body is manifested by the following features:

1. Headache, dizziness, anorexia, nausea, vomiting and mental confusion - due to cerebral edema.
2. Convulsion and coma of death - due to severe water intoxication.

Diagnosis

1. Considering the circumstances in which water intoxication is likely to occur
2. Plasma Na^+ below 130mmol/l.

Management

1. Water restriction. Daily intake of water volume should be equal to urinary output+ 400ml for insensible loss.
2. Treatment of the cause.
3. In severe symptomatic cases 100ml of 5% NaCl solution should be given I/V and repeated in a few hour if there is little or no improvement and the plasma Na^+ remains below 130mmol/l.

SODIUM AND WATER EXCESS

Aetiology

1. Nephrotic syndrome, acute oliguric renal failure.
2. Congestive cardiac failure.
3. Hepatic cirrhosis, acute hepatic failure.

CONDITIONS ASSOCIATED WITH GENERALISED OEDEMA

- Congestive cardiac failure
- Hepatic cirrhosis, acute liver failure, hepatic vein thrombosis
- Acute oliguric renal failure, advanced chronic renal failure (GFR < 15 ml/min), acute nephritic syndrome, nephrotic syndrome
- Protein-losing gastroenteropathy
- Starvation, thiamine deficiency
- Pregnancy, premenstrual
- Acute anaphylaxis
- Drugs which induce renal Na^+ retention:
  Antihypertensives (particularly vasodilators), corticosteroids, liquorice, carbenoxolone, oestrogens, NSAID

Clinical features

- Oedema

Management

MANAGEMENT OF OEDEMA

- Measures designed to correct specific factors causing oedema, e.g. corticosteroids in steroid sensitive nephropathy; salt poor albumen in hypoproteinaemia; rest, vasodilators, digoxin in heart failure
- Restriction of dietary Na^+ to about 100 mmol/day ('no added salt diet') in mild and moderate cases or 50 mmol/day in severe resistant cases
- Diuretics to increase rate of urinary excretion of Na^+ and water

Diuretic therapy

Mild Oedema

a) Moderate salt restriction plus
b) Thiazide diuretics e.g. Hydrochlorothiazide (moduretic) 50-10mg/day.

Moderate to severe oedema

Frusemide (Lasix) 40-120mg/day orally or 20-40mg I/V. K^+ supplement should always be given with frusemide because frusemide causes hypokalemia.

Resistant oedema

In patients with resistant oedema due to cirrhosis or severe cardiac failure whose renal function is normal, a combination of spironolactone (100-200mg) or amiloride (20mg) with frusemide (Lasix) may induce diuresis. When severe hypoproteinemia is present, addition of salt free albumin in the regime usually induces diuresis.

CAUSES OF RESISTANCE TO THE EFFECTS OF DIURETICS

- Reduced renal blood flow. GFR < 20 ml/min
- Severe hypoproteinaemia
- Severe secondary aldosteronism

POTASSIUM DEPLETION

Causes of hypokalaemia.

Intracellular shifts
Alkalosis
High-dose insulin
Periodic paralysis (see p. 963)

Extra renal loss
Diuresis
  Drugs
  Osmotic (e.g. hyperglycaemia, uraemia)
Renal tubular acidosis
Hyperaldosteronism—primary or secondary
Cushing's and adrenogenital syndromes
Bartter's syndrome
Drugs (e.g. liquorice, carbenoxolone sodium, gentamicin toxicity)
Leukaemia

Gastrointestinal loss
Vomiting and diarrhoea
Ileostomy or ureterosigmoidostomy
Purgative abuse
Anorexia nervosa with bulimia
Villous adenoma of rectum

CLINICAL FEATURES OF ACUTE POTASSIUM DEPLETION (DEFICIT > 10% BODY K^+)

Causes
Loss of large volumes of intestinal secretions, massive diuresis following relief of urinary tract obstruction, severe ketoacidosis

Associated disturbances
Severe Na^+ and water depletion, commonly metabolic acidosis, possible Mg^{++} depletion

Presentation
Initially features of ECF depletion predominate (p. 206) and plasma [K^+] may be normal
When ECF volume restored unless K^+ salts are given plasma [K^+] falls and features of acute K^+ depletion develop viz:
  Generalised muscle weakness, depression of tendon reflexes
  ECG changes (Fig. 6.7), arrhythmias, sensitivity to digitalis, reduced cardiac output
  Paraesthesiae, apathy, confusion, coma
Death may occur due to respiratory paralysis or cardiac arrest

Diagnosis
On basis history, clinical findings
Low plasma [K^+] confirms diagnosis (plasma [K^+] may be normal at presentation)

PREVENTION OF POTASSIUM DEPLETION

- Patients receiving benzothiadiazine diuretics, frusemide or bumetanide for treatment of oedema should receive KCl 20–60 mmol/day in whatever form is tolerated. Plasma [K^+] should be monitored at intervals and the dose adjusted.
- Some patients receiving pharmacological doses of corticosteroids require KCl supplements.
- Patients receiving diuretics for treatment of hypertension may require KCl supplements.
- Patients unable to eat or drink, maintained on i.v. fluids, should receive sufficient KCl, distributed through the fluids, to maintain K^+ balance. 60–80 mmol/day is recommended for patients with no unusual K^+ loss. The plasma [K^+] should be monitored at least daily and the dose adjusted.

POTASSIUM EXCESS

Causes of hyperkalaemia.

Excessive intake

Impaired renal excretion
Oliguric renal failure
Potassium-sparing diuretics, e.g. amiloride
Adrenal insufficiency
Renal tubulo-interstitial disease
ACE inhibitors, e.g. enalapril

Loss of potassium from cells
Acidosis
Crush injury, rhabdomyolysis, burns
Tumour therapy
Suxamethonium

CIRCUMSTANCES IN WHICH SIGNIFICANT HYPERKALAEMIA MAY OCCUR

- Tissue damage with release of K^+ from dead and injured cells
- Rapid administration of a large amount of K^+ by mouth or i.v.
- Impaired renal excretion of K^+ including administration of potassium-sparing diuretics such as spironolactone
- Combination of lesser degrees of points 1 and 2 with 3

MANAGEMENT OF ACUTE HYPERKALAEMIA

- Identify and if possible remove the cause
- When there are marked ECG changes inject 10 ml 10% calcium gluconate solution slowly, monitoring ECG throughout.
- Inject 50 ml 50% glucose +5 units soluble insulin i.v. to encourage shift of K^+ into cells. Monitor plasma [K^+] at intervals and repeat procedure if hyperkalaemia recurs. Alternatively 500 ml of 20% glucose solution +5–10 units soluble insulin are infused over 6–12 hours.
- Infuse 1.26% $NaHCO_3$ solution until plasma [HCO_3^-] is in the upper reference range to encourage shift of K^+ into cells and excretion of K^+ in urine. This must not be done if there is evidence of circulatory overload.
- Replace any Na^+ and water deficit to restore circulation, renal perfusion and K^+ excretion.
- Correct respiratory acidosis.
- If these measures fail haemodialysis or peritoneal dialysis is indicated.

MAGNESIUM DEPLETION

Causes of hypomagnesaemia.

Decreased intake
Starvation
Prolonged parenteral feeding

Decreased gut absorption
Small gut disease
Extensive small gut resection

Gut losses
Prolonged nasogastric suction
Excessive purgation
Gastrointestinal/biliary fistula
Severe diarrhoea

Excessive urine losses
Diuretic states due to:
- Loop diuretics
- Post obstruction
- Recovery phase of acute tubular necrosis
- Hyperglycaemia
- Diabetic ketoacidosis

Renal tubular acidosis
Chronic alcohol consumption
Gentamicin toxicity
Primary aldosteronism
Hypothyroidism

Acute pancreatitis

Left blank intentionally

Pharmacology

PROPRANOLOL (INDERAL)

Indications:
1. Hypertension.
2. Angina Pectoris
3. Arrhythmias: Digitalis induced arrhythmias, Wolff Parkinson white syndrome.
4. Atrial Fibrillation and Flutter.
5. Tachycardia in mitral stenosis, thyrotoxicosis.
6. Myocardial infarction.
7. Pheochromocytoma (with alpha-2 blockers).
8. Anxiety and tremors.
9. In alcohol withdrawal.

Side effects:
1. Asthma.
2. Congestive cardiac failure.
3. Hypoglycemia.
4. CNS disturbances (Lethargy, poor concentration, feeling of coldness, sleep disturbances).
5. Allergic reactions.

Contra-Indications
1. Bronchial Asthma.
2. Congestive cardiac failure.
3. Partial heart block.
4. Hypertension.

ISONIAZID (INH)

Indication:
Tuberculosis

Adverse effects:
Peripheral neuropathy.
Toxicity: Insomnia, difficulty in concentration, impairment of memory, in-co-ordination, epilepti-form seizures, difficulty with micturition, muscle twitching.

Allergy: Hepatitis, eczema, bone marrow hypoplasia, fever and lymphadenopathy.

RIFAMPICIN

Adverse effects:
Toxicity: Hepatotoxicity, GIT disturbances.

Allergy: Skin rashes, mild leucopenia, thrombocytopenia, hemolytic anaemia and renal failure.

CHLOROQUINE (RESOCHIN)

Indications:
1. Malaria.
2. Amoebic hepatitis.
3. Giardiasis.
4. Rheumatoid arthritis.

Side effects:
1. Retinal damage and corneal opacities, retinopath
2. Headache, nausea, vomiting.
3. Hemolytic anaemia in glucose-6-phosphate de hydrogenase deficiency and neutropenia.
4. Pruritis, lichenoid dermatitis and alopecia.
5. Hypotension - if given I/V.
6. Mutagenic and carcinogenic.

METRONIDAZOLE (ABOZOLE)

Indications:
1. Severe intestinal infection in amoebiasis.
2. Extra intestinal amoebiasis.
3. Gum infection

Adverse effects:
1. Metallic taste.
2. Nausea, vomiting, diarrhoea and headache.
3. Rarely stomatitis, leucopenia, rashes, pruritis.

HEPARIN

Indications:
1. To prevent clotting in open heart surgery and in hemodialysis
2. Post-operative deep venous thrombosis and pulmonary embolism.
3. Disseminated intravascular coagulation.
4. For primary prophylaxis of thromboemblosim after acute myocardial infarction.

Side effects:
1. Haemorrhage.
2. Hypersensitivity
3. Osteoporosis
4. Acute thrombocytopenia
5. Alopecia.

FRUSEMIDE (LASIX)

Indications:
1. Acute pulmonary oedema
2. Oedema due to pulmonary or renal disease or due to congestive cardiac failure.
3. Acute or chronic renal failure.

Side Effects:
1. Hypotension
2. Hypovolemia.
3. Hypokalemia.
4. Hypoantraemia.
5. Hyperuricemia.
6. Hyperglycemia.
7. GIT disturbances.
8. Thrombocytopenia - skin rashes.

PARACETAMOL (PANADOL)

Indications:
1. Superficial pain.
2. Fever.

Side effects:
1. Skin rashes.
2. Hepatic necrosis.
3. Acute tubular necrosis.

ASPIRIN

Indications:
1. Fever.
2. Headache, toothache, muscular and joint pain.
3. Gout.
4. Rheumatoid arthritis.
5. Salicylic acid is used topically as keratolytic and as antifungal agent.
6. Methyl salicylic acid is used in the form of ointment for painful muscles or joints. (Iodex)

Side effects:
1. Epigastric discomfort.
2. GIT Bleeding.
3. Salicylism: This is mild salicylic acid intoxication:
   Symptoms: Headache, confusion, deafness, ringing in the ear, dimness of vision, sweating, hyperventilation, nausea, vomiting and diarrhoea.
4. Acute Salicylic acid poisoning: symptoms are:
   - CNS: restlessness, convulsion, coma.
   - Skin eruptions.
   - Anorexia, nausea, vomiting.
   - Haemorrhage due to hypoprothrombinemia.
   - Hyperpyrexia.
5. Aspirin Hypersensitivity (Urticaria, Asthma).
6. Respiratory failure.

CHLORPROMAZINE (LARGACTIL)

Indications:
1. Psychosis e.g. schizophrenia.
2. Vomiting.
3. Hiccough.
4. As preanesthetic medication.
5. As antipruritic agent to relieve itching.

Side effects:
1. Parkinsonism.
2. Jaundice.
3. Lethargy.

4. Purplish discoloration of skin.
5. Hypersensitivity dermatitis.
6. Photosensitization.
7. Gynecomastia.

CIMITIDINE (TAGAMET)

Indication:
Peptic ulcer

Side effects: It is a safe drug, however may produce:
1. Mild diarrhoea.
2. Gynecomastia.
3. Impotence.
4. Drowsiness.
5. Itching, skin rashes.

SALBUTAMOL (VENTOLIN)

Indications:
Bronchial asthma.

Side effects:
Muscle tremor and palpitation when given orally in high doses. Side effects absent when used by inhalation.

NITROGLYCERINE (ANGESID)

Indications:
Angina pectoris.

Adverse effects:
1. Headache.
2. Flushing.
3. Postural hypotension.
4. Dizziness.
5. Unconsciousness.

METHYLDOPA (ALDOMET)

Indications:
Moderate to severs hypertension

Side effects:
1. Sedation, parkinsonism, dizziness.
2. Nausea, vomiting, diarrhoea.
3. Bradycardia, nasal stuffiness.
4. Jaundice, hemolytic anaemia.
5. Hypersensitivity reactions.
*6. Retrograde ejaculation (impotence)

Contra Indications:
Pheochromocytoma

DIGOXIN

Indications:
1. Congestive cardiac failure.
2. Atrial fibrillation.
3. Atrial flutter.
4. Paroxysmal supraventricular tachycardia.

Contra Indications:
1. Ventricular tachycardia.
2. Along with calcium or sympathomimetic.

Toxic effects:
1. *Git effects:* Anorexia, nausea, vomiting, diarrhoea and abdominal pain.
2. *Neurological effects:* Headache, fatigue, malaise, drowsiness, disorientation, aphasia, delirium, hallucination and blurred vision.
3. *Cardiac effects:*
   - Ventricular tachycardia.
   - Multiform ventricular extrasystole.
   - Paroxysmal atrial tachycardia.
   - A-V heart block.

NIFEDIPINE (ADALAT).

Indications:
1. Angina of effort.
2. Hypertension.
3. Acute left ventricular failure.

Side effects:
Headache, flushing and palpitation due to peripheral vasodilation.

VERAPAMIL (CALAN)

Indications:
1. Angina.
2. Supraventricular tachycardia.
3. Paroxysmal supraventricular tachycardia.
4. Atrial flutter and fibrillation.
5. Hypertension.

Side effects:
1. Constipation, flushing, headache, nausea, vomiting and allergic reactions when given orally.
2. Sinus bradycardia sinus arrest, hypotension and heart block when given intravenously.

Contra indications:
1. Heart block
2. Hypotension.
3. Digitalis toxicity.

INSULIN

Transparent - short acting
Cloudy - long acting

Indications:
1. Insulin dependent diabetes mellitus
2. Diabetic ketoacidosis

Adverse effects:
1. Hypoglycaemia
2. Local skin allergy
3. Local fat atrophy at the site of injection.
4. Insulin resistance.
5. Obesity

PHENYTOIN

Indication:
Epilepsy

Side effects:
1. Hyperplasia of the gum.
2. Nystagmus.
3. Dizziness, nausea, skin rashes, insomnia.
4. Ataxia & tremors.

PRESCRIPTIONS

PRESCRIPTION WRITING

Rx
Name
Age

General

- Diagnosis
- Diet: such as low salt diet, low fat diet
- Activity: routine activity, avoid exertion, bed rest

Specific and symptomatic

- Such as antibiotic for pneumonia: main drug
- Paracetamol for fever: symptomatic
- Cough syrup: symptomatic

Components of prescription

Prescription should have the following components:

- Write whether the drug is tablet, capsule, injection or syrup.
- Write the clear name of drug because certain drugs are similar in spelling such as Encid and Ansaid and the patient may get wrong drug from pharmacy.
- Write the strength of drug such as 5mg, 10mg etc.
- Mention the route of administration e.g. oral, subligual, local.
- Write the frequency of medication such as 6-hourly, 12 – hourly.
- Now write the duration of treatment e.g. for 7 days.
- Relation with food should be mentioned such as ATT should be taken in fasting before breakfast.
- Mention about next appointment.

DR. SAEED –UR- REHMAN
FCPS
Consultant physician
Tel # 9215740

Name: Syed Shahid Ali *Age:* 46 years

Weight: 62 kg *Date:* 15-9-2001

Contact # 4560001

Diagnosis: Reflux esophagitis

General

- Reduce weight
- Avoid smoking, fatty meal, coffee, citrus fruits
- Take small meals, do not lie for 2 hours after meal
- Elevate head end of the bed

Specific

1. Cap. Zoton (Lansoprazol) 30mg orally
   1+0+0
   One hour before meal for 2 weeks

2. Tab. Motilium (Dompeidone)
   1+1+1
   One hour before meal

3. Syp. Mucaine (antacid)
   2 teaspoonful 20 min before meal
   (But do not use with the Cap. Zoton)

Review after 4 weeks on 15-10-2001 at 6: 30 p.m.

Signature

xyz

MALARIA

Chloroquine sensitive malaria
Tab. Chloroquine phosphate (Resochin) 250mg orally
4 tab. once (stat)
2 tab. after 6hours
1tab twice daily for 2days

chloroquine resistant / Falciparum malaria

Parenteral drugs:
Inj. Artemether (Artem) 80mg I/M
2 injections (160mg) once (stat)
one injection (80mg) daily for 4 days.

Alternative
Inj. Quinine sulphate 600mg IV
Dilute in 300-500ml of dextrose water given over a operiod of 4 hours every 8 hourly for 7-10 days.

Oral drugs:
Use one of the following:

- Cap. Artemether (Artem) 40mg orally
  2 cap. Daily for 7days.
- Tab Fensidar (a combination of sulfonamide and diaminopyridine)
  3 Tab. As a single dose orally.
- Tab. Exafal (a combinaion of artemether and lumefantrine)
  4 tab. at 0, 8, 24 and 48 hours.

Antimalarial used in pregnancy
Chloroquine, quinine

Antimalarial contraindicated in pregnancy
Artem, Exafal, tetracycline, Halfan and doxycycline.

TYPHOID

Patient over 17 years.

Tab. Ciprofloxacin (Tarivid) 500mg orally
1+0+1 for 2 weeks

Tab. Paracetamol (Calpol) 500mg
2+2+2+2

Patient under 17 years
Cap. Cefixime (Cefspan) 400mg orally
1+0+1 for 2 weeks
OR

Amoxicillin (Cap. Amoxil 500mg)
2+2+2+2 for 2 weeks

Hospitalized patient
Ceftriaxone (Rocephin 1g) 2-4g IV once daily for 3 days.

TUBERCULOSIS

Weight =50
All tablets one daily before breakfast

- Tab. INH 100 mg 3 OD
- Tab. Rifampicin 450 mg 1 OD
- Tab. Ethambutol 400 mg 3 OD
- Tab. Pyrazinamide 500 mg 3 OD
- Tab. Pyridoxine (vit B6) 50 mg OD

Drug	Dose mg/kg	<33 kg	33-50 kg	>51 kg
Isoniazid	5 maximum 300mg/day	200	300	300
Rifampicin	10	300	450	600
Ethambutol	15-25	800	1200	1600
Pyrazinamide	15-30	1000	1500	2000
Streptomycin	15	500	750	1g

Secrets of Examination

The basic problem which our students face during their studies & examinations is lack of guidance. That is the reason why despite having sound knowledge about the subject, they fail to gain a good score.

Here are some tips to remember to Improve your scoring in your final year examinations.

Pattern of Study:

The pattern of study at the undergraduate level is quite different from that at the postgraduate level. At the undergraduate level importance is given to the diseases that are common in our region. While at the PG level thorough knowledge of the subject is required. So you should have comprehensive knowledge of the diseases for final year examination that are common in our part of the world.

Following are the modalities of your examination:

1) Long case — One
2) Short Case — Two
3) Table Viva — Instruments, Pathology specimens, X-rays, drugs & general discussion.

Long Case

There will be one long case allotted to each student. List of the important long cases is given below. Prepare these cases as thoroughly as possible.

It would be better if you take a round of your medical ward before the examination to have a look at the cases present there. Try to study the patients, this will prove a great help to you.

While preparing for the long case you are also supposed to know the D/D of the complaints related to the case.

Say for example, you get a case of peptic ulcer; in addition to the causes, signs & symptoms of the disease you should also know other conditions that can mimic the disease and can produce similar symptoms.

Sometimes the panel of examiners comprises examiners from other specialities of medicine e.g., neuro medicine, chest medicine etc. They put special emphasis on history taking and judge the student on the basis of this history taking. Remember a golden rule that "Good history can score you good marks". So try to take a good history of your case.

Do not READ the history to the examiner, try to recite it. It will give a good impression.

Write your diagnosis, regardless of being right or wrong. But you should be able to defend your diagnosis.

When the examiner asks you about your diagnosis, do not tell him the diagnosis straight away, rather say "on the basis of history & examination my diagnosis is xyz" then the examiner will ask you about your history and findings on examination.

Always tell the examiner the positive findings of your general examination first e.g., the patient presents with anemia and lymphadenopathy. First state the patient's vital signs i.e. pulse, B.P., temperature and respiration then state that "anemia and lymphadenopathy are positive, while the rest of the findings are negative". Be careful to choose the right words and right statements while presenting your case.

Now we came on the systemic examination.

While writing about the systemic examination, write the system first which according to the patient's complain seems to be involved most e.g. if patient presents with pain in epigastruim, hematemesis, abdominal distention, gastrointestinal tract involvement seems to be most possible so you should do a thorough GIT examination with inspection, palpation, percussion and auscultation.Other systems should be described briefly.

IMPORTANT LONG CASES

1. **Gastroenterology**
   - Peptic ulcer
   - Malabsorption
   - Abdominal tuberculosis

2. **Liver**
   - Acute viral hepatitis (Jaundice)
   - Cirrhosis
   - Obstructive Jaundice
   - Hepatoma
   - Liver abscess

3. **Respiratory system**
   - Tuberculosis
   - COPD
   - Asthma and bronchiectasis
   - Pneumonia
   - Bronchial carcinoma

4. **Cardiovascular System**
   - Cardiac failure
   - Mitral stenosis and regurgitation

5. **Endocrinology**
   - Diabetes mallitus
   - Hypothyroidism and hyperthyroidism
   - Obesity

6. **Rheumatolgoy**
   - Rheumatoid arthritis
   - SLE
   - Septic arthritis

7. **Kidney**
   - Chronic renal failure
   - Nephrotic syndrom

CNS
- Stroke (CVA)
- Cranial nerve palsies
- Meningitis

. **Blood**
- Anemia (iron deficiency anemia)
- Leukaemia

10. **Infectious diseases**
    - Typhoid
    - Malaria
    - Dysentery
    - Food poisoning
    - Amoebic dysentery
    - Filariasis

SHORT CASES

There will be two short cases allotted to each student. List of the Important short cases is given below. Prepare them thoroughly.

1. General physical examination
2. Examination of GIT
3. Examination of respiratory system.
4. Examination of CVS
5. Examination of Motor system or Cranial nerves

General physical examination

The patients may be having any of the following feature and the viva will be based on the findings of the patient.

i. Anemia: Causes of anemia, especially iron deficiency anaemia.
ii. Clubbing: Causes especially Bronchogenic carcinoma and T.B.
iii. Purpose: Causes of thrombocytopenia and other coagulation disorders.
iv. Jaundice
v. Pigmentation

2. Examination of GIT:
- Clinical Methods of palpation of liver, spleen, and kidney.
- Percussion of abdomen
- Fluid thrill and shifting dullness.
- Causes of positive findings and related discussion.

3. Examination of Respiratory System

Mostly the cases are of COPD, T.B. and Pleural effusion and the students are asked to percuss and auscultate the chest.

4. Examination of CVS

Students may be asked to:
- Examine the JVP.
- Palpate the peripheral pulses

Auscultate any murmur or additional sound. Mostly the cases are of mitral stenosis and regurgitation.

5. **Examination of Motor System**
   Usually the case is of upper motor neurone lesion. Procedure of eliciting reflex, and of checking tone is examined.
   Cranial Nerve: Usually procedures of oclumotor & facial nerve tests are examined.

TABLE VIVA

1. **Instruments:**
   Table viva is usually started with instruments, therefore they should be prepared thoroughly. Instruments should be studied under there modalities
   - Indications
   - Contraindications
   - Complications

Examiner usually ask the student to pick any instrument and then the viva proceeds with the discussion related to the iInstrument. For example if the student is asked to pick the L.P needle then the questions related to menangitis may also be asked. So prepare all the instruments thoroughly.

2. **Pathology Specimens:**
   Mostly the specimen are
   1. Liver
   2. Spleen
   3. Ascaris
   5. Tenia

3. **Drugs:**
   - Indications
   - Side effects

4. **X-Rays:** Common X-rays are
   - Pleural effusion
   - T.B.
   - Cardiomegaly
   - Bronchogenic carcinoma

PSYCHOLOGICAL ASPECTS OF THE EXAMINATION

- Stop all your studies at 11 p.m. a night before the examination
- Relax yourself and try to have a sound sleep. If you are anxious and could not sieep then take a tab. Dormicum. It is a rapid sleep inducer and has no hangover (drowsiness). On waking you will feel fresh and alert next morning. You must enter the examination hall with fresh mind.
- Your dress should be neat and clean, shoes should be polished and hair should be properly combed.
- Don't forget to bring with you, your stethoscope, torch, hammer, measuring tape, pen and neat and clean white coat.

HOW TO APPROACH THE EXAMINER

When your number is called, first *Salam* the examiner, then ask the permission to sit down.

1. Try to answer all the questions with confidence. If you don't know the answer tell the examiner you don't know. He may then moveto another question.
2. Never try to provoke the examiner during the examination.
3. Try to remain calm, listen every question carefully & take your time to answer it.
   If you follow these tip I am confident that you will improve your scoring a lot.

Wish you all the best.

Inaam Danish

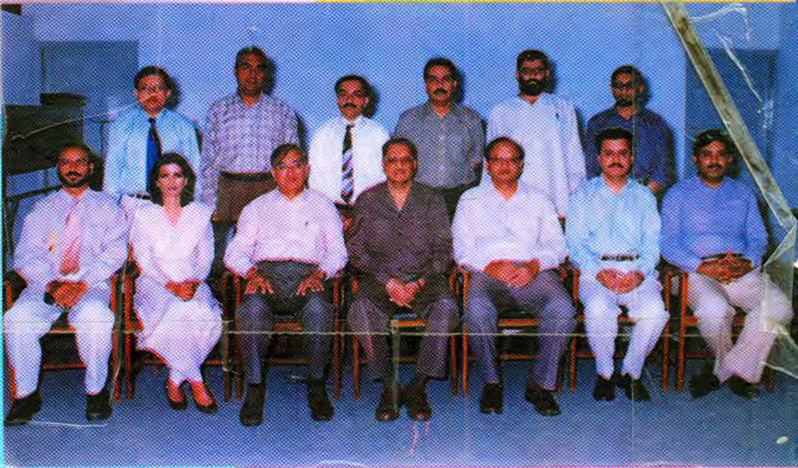
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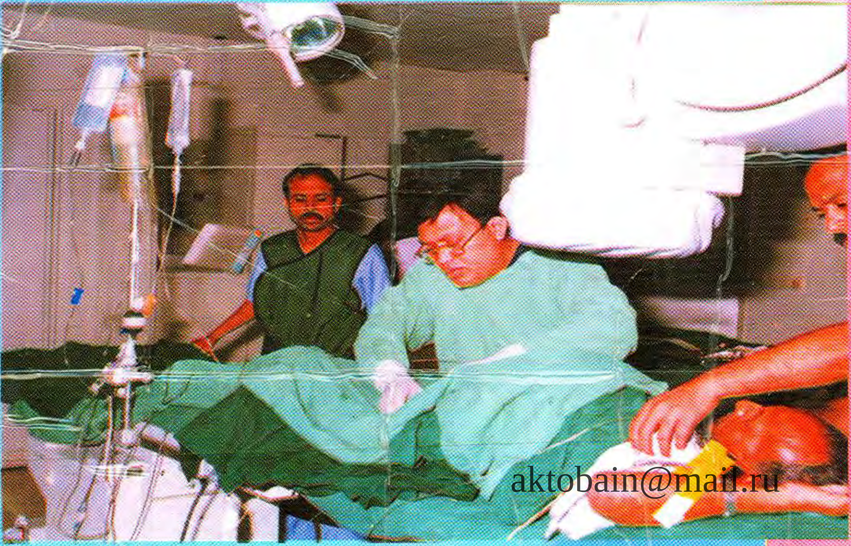


Dr. Mohammad Inam Danish is one of the pioneer in medical publication writing in Pakistan. He started writing when there were no proper publications on medical subjects in the country.

He is graduate of 1991 from Sindh Medical College Karachi. In 1987 his first handbook was published on Physiology (when he was in 2nd year MBBS), this book became very popular among the medical students all over the country. Then he published Pharmacology, Toxicology and Pathology. All these books were appreciated by medical students.

Short Textbook of Medical Diagnosis and Management was first time published in 1992; since then this is the only Pakistani favorite short book on medicine that is helping students all over the world. Please send your comments and positive criticism to improve it further.





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